FORMULATION DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE BILAYER FLOATING TABLETS OF ROSUVASTATIN CALCIUM AND CARVEDILOL

A Dissertation submitted to

THE TAMIL NADU Dr. M.G.R MEDICAL UNIVERSITY

CHENNAI – 600 032

in partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY

submitted by

Register Number: 261411266

under the guidance of

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COLLEGE OF PHARMACY
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APRIL – 2016

DEPARTMENT OF PHARMACEUTICS
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DATE:

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Place: Chennai – 03

Date:

(Dr. A. JERAD SURESH, M.Pharm., Ph.D., M.B.A)

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(K Elango,M.Pharm.,(Ph.D.))

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CONTENTS

ABBREVIATIONS

GRDDS	Gastro Retentive Drug Delivery Systems
GIT	Gastro Intestinal Tract
GRT	Gastric Retention Time
FDDS	Floating Drug Delivery System
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CAD	Coronary Artery Disease
ACE	Angiotensin Converting Enzymes
HDL	High Density Lipoproteins
LDL	Low Density Lipoproteins
VLDL	Very Low Density Lipoproteins
TG	Triglycerides
MMG	Migrating Myloelectric Cycle
HPMC	Hydroxy Propyl Methyl Cellulose
PVP	Poly Vinyl Pyrrolidone
SSG	Sodium Starch Glycolate
CCS	Cros Carmellose Sodium
ARB	Angiotensin Receptor Blocker
PPAR	Peroxisome Proliferator-Activated Receptor-gamma
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
ROS	Rosuvastatin Calcium
CAR	Carvedilol

BFT	Bilayer Floating Tablets
ICH	International Conference on Hormonisation
IR	Immediate Release
SR	Sustained Release
HCl	Hydrochloric acid
mmHg	Mercuric millimeter
mg	Milligram
mL	Milliliter
µg	Microgram
%	Percentage
RPM	Revolution Per Minute
FTIR	Fourier Transform Infra-Red
RH	Relative Humidity

ORAL DRUG DELIVERY SYSTEM[1]

A drug can be administered through various routes to produce prompt pharmacological effect. An oral delivery is considered as most favoured route of delivery in the pharmaceutical industry.

This is due to following reasons:

- Oral route is most convenient and uncomplicated
- Ease of administration and safe
- Improved patient compliance
- Cost-effective

Oral solid dosage forms such as tablets and capsules have been formulated and developed nowadays since they are the most effective routes of administration of a new drug. Nevertheless, it is probable that at least 90% of all drugs used to produce systemic effects are administered by the oral route. Tablets and capsules represent unit dosage forms in which one usual dose of the drug has been accurately placed.

TABLETS

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. They vary in shape and different greatly in size and weight, depending on amount of medicinal substance and the intended mode of administration. Tablet may be coated or uncoated, consist of one or more active substances with or without excipients such as diluents, binders, disintegrating agent, glidants, lubricants, substances capable of modifying the behaviour of the preparation indigestive tract, colouring matter authorized by the component authority and flavouring substances. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of tablet.

ADVANTAGES[2]

- They are the unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest precision and least content variability.
- Low cost among all oral dosage forms.
- They are the easiest and cheapest to package and ship.
- Product identification requires no additional processing steps when employing embossed or monogrammed punch face.

- Provides greatest ease of swallowing with the least tendency for hang up above the stomach, especially when provided the tablet disintegration is not excessively rapid.
- They lend themselves to certain special release profile products E.g. enteric coated or delayed release profiles.
- Easy large scale production than other oral dosage forms.
- They have the best combined properties of chemical, mechanical and microbiological stability among all the oral dosage forms.
- The emergency supplies of the drug can be conveniently carried by the patient.

DISADVANTAGES:

- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low density character.
- Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the gastro intestinal tract or any combination of this features may be difficult or impossible to formulate and manufacture as tablet that will still provide adequate or full drug bioavailability.
- Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression, or the tablets may require coating. In such cases, the capsules may offer the best and lowest cost approach.

TYPES OF TABLET:

Tablets are divided into classes based on their route of administration and their function.

1. TABLETS ADMINISTERED ORALLY:

A. COMPRESSED TABLETS

- Sugar coated tablets
- Film coated tablets
- Enteric coated tablets
- Chewable tablets
- Controlled release tablets

B. MULTIPLE COMPRESSED TABLETS

- Layered tablets
- Press coated tablets

C. TABLETS ADMINISTERED IN ORAL CAVITY

- Buccal and sublingual tablets
- Lozenges and troches
- Dental cores

2. TABLETS ADMINTERED VIA OTHER ROUTES:

- Implants
- Compressed suppositories or inserts
- Vaginal tablets

3. TABLETS ADMINISTERED IN SOLUTION FORM

- Effervescent tablets
- Dispensing tablets
- Hypodermic tablets
- Tablet triturates

LAYER TABLETS[3]

Layer tablets are composed of two or three layers of granulation compressed together. As the edges of each layer are exposed they have the appearance of a sandwich. This dosage form has the advantage of separating two incompatible substances with an inert barrier between them. It makes possible sustained-release preparations with the immediate-release quantity in one layer and the slow release portion in the second. A third layer with an intermediate release might be added.

Multi-layer tablet dosage forms are designed for variety of reasons which are as follows:

- ✓ To control the delivery rate of either single or two different active pharmaceutical ingredients.
- ✓ To separate incompatible active pharmaceutical ingredients from each other to control the release of active pharmaceutical ingredient from one layer by utilizing the

functional property of the other layer such as, different active pharmaceutical ingredients, to prolong the drug product life cycle.

- ✓ To modify the total surface area available for active pharmaceutical ingredients layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release.
- ✓ To fabricate novel drug delivery systems such as chewing device, buccal / mucoadhesive delivery systems and floating tablets for gastro-retentive drug delivery

BILAYER TABLETS

Bilayer tablets are composed of two layers of granulation compressed together. Two-layer tablets require fewer materials than compression-coated tablets weigh less and may be thinner. Monograms and other distinctive markings may be impressed in the surfaces of the multilayer tablets.

Coloring the separate layers provides many possibilities for unique tablet identity. Separation of the layers prior to assay may simplify the analytical work. Since there is no transfer to a second set of punches and dies, as with the dry-coating machine, odd shapes (such as triangles, squares, and ovals) present no operating problems except for those common to keyed tooling Several pharmaceutical companies are currently developing bilayer tablets, for a variety of reasons viz. patent extension, therapeutic, marketing to name a few.

ADVANTAGES:

- ➢ Ability to combine different release rate such as IR and CR in the same tablet for chronic conditions requiring the repeated dosing.
- ➢ Improves patient compliance
- ➢ Prolong duration of action
- ➢ Better plasma drug level can be achieved
- ➢ Retain potency and ensure dose accuracy
- ➢ Maintain physical and chemical stability

CHALLENGES IN BILAYER MANUFACTURING

Conceptually, bilayer tablets can be seen as two single-layer tablets compressed into one. In practice, there are some manufacturing challenges.

- **Delamination:**

  Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.

- **Cross-contamination:**

  When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. It may conquer the very purpose of the bilayer tablet. Proper dust collection goes a long way toward preventing cross contamination.

- **Production Yields:**

  To prevent cross contamination, dust collection is required which leads to losses.Thus, bilayer tablets have lower yields than single-layer tablets.

- **Cost:**

  Bilayer tableting is more expensive than single-layer tableting for several reasons:

  - The tablet press costs more.
  - The press generally runs more slowly in bilayer mode.
  - Development of two compatible granulations is must, which means more time spent on formulation development, analysis and validation

These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per se and the quality attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control). Therefore, it is critical to obtain an insight into the root causes to enable design of a robust product and process.

QUALITY AND GMP REQUIREMENTS:

To produce a quality bilayer tablet in a validated and GMP manner, it is important that the selected press is capable of:

- ✓ Preventing capping and separation of the two individual layers that constitute the bilayer tablets.
- ✓ Providing sufficient tablet hardness.
- ✓ Preventing cross -contamination between the two layers.
- ✓ Producin a clear visual separation between the two layers.
- ✓ High yield accurate and individual weight control of the two layers.

APPLICATIONS

- ➢ Bi-layer tablet is suitable for sequential release of two drugs in combination
- ➢ Separate two incompatible substances.
- ➢ Promoting patient convenience and compliance.
- ➢ Bilayer tablet is improved beneficial technology to overcome the short coming of the single layered tablet.
- ➢ Bilayer tablets are used to deliver the loading dose and sustained dose of the same or different drugs.
- ➢ Bilayer tablets are used for bilayer floating tablets in which one layer is floating layer and another one is immediate release layer of the drug.

CONTROLLED DRUG DELIVERY SYSTEMS (CDDS)[4]

Controlled release drug delivery system was designed to deliver for a prolonged period. Safe and effective blood levels are maintained for longer period as the system continues to deliver the drug. Controlled drug delivery usually results in constant blood levels of the drug as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.

Advantages

Controlled release products offer many potential benefits over conventional dosage formulations, they are

- Sustained blood levels
- Dosage frequency reduction
- Improve patient compliance
- Improve efficiency in treatment
- Economy i.e. reduction in health care costs etc.

Disadvantages

- Controlled release products contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form has potential problems.
- The larger size of sustained release sustained release products may cause difficulties in ingestion or transit through the gut.
- Sustained release products may cause decreased systemic bioavailability in comparison to conventional dosage forms, which may be due to incomplete release, increased first pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
- Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus increased risk of toxicity.

GASTRORETENTIVE DRUG DELIVERY SYSTEMS[5,6]

Dosage form with a prolonged gastric residence and controlled drug delivery are called as GRDDS. Oral controlled release dosage forms are developed due to their therapeutic advantages such as patient compliance, ease of administration and flexibility in formulation. However this approach has several physiological difficulties such as inability to locate the dosage form at the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying time. The gastric emptying time in human normally ranges from 2-3 hours through which the major absorption zone (stomach and upper part of intestine) passes through that so the dosage form can result in incomplete drug absorption from the delivery system and leading to reduced efficacy of the administered dose. Therefore the control of placement of a drug

delivery system in a specific region of the GIT offers greater advantage. The drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem in the intestine can be benefitted by this approach. These have led to the development of a unique oral controlled release dosage form with gastro retentive properties.

After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper GIT.

ANATOMICAL AND MECHANICAL ASPECTS OF STOMACH[7]

A basic understanding of the anatomical and mechanical aspects of the stomach is needed for a pharmaceutical formulator to develop successful gastro retentive formulation.The stomach is divided into 4 regions are the cardia, fundus, body and pylorus.

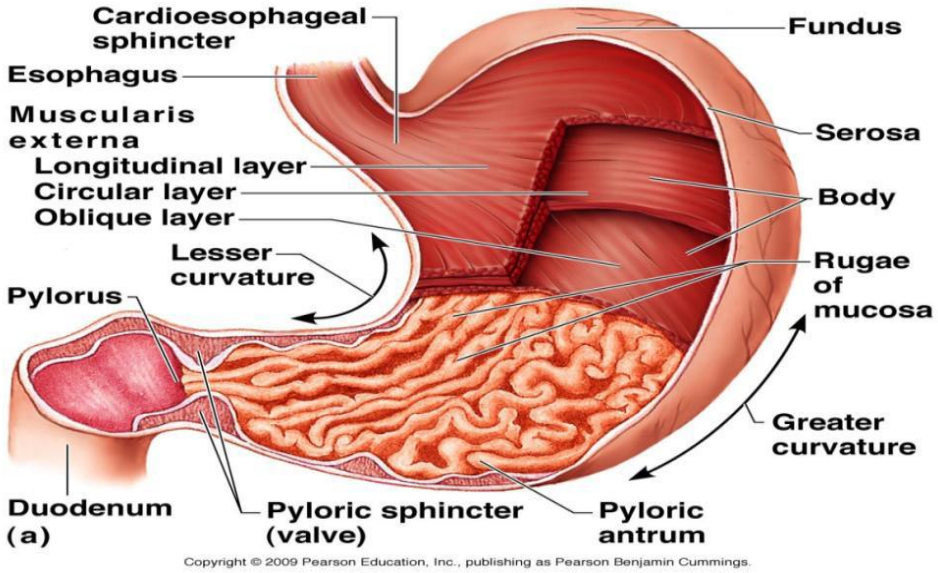


Fig. 1:Anatomical representation of the stomach

The process of gastric emptying occurs both during fasting and fed states. The pattern of motility differs markedly in the two states. In the fasted state it is characterized by an inter-digestive series of electrical events which cycle both through the stomach and small intestine for every 2-3 hours.

Gastric emptying is divided into 4 phases are as following:

This is called the inter-digestive myoelectric cycle or migrating myoelectric cycle (MMC) which is further divided into following 4 phases as described by Wilson and Washington.

- ❖ Phase I(Basel phase) lasts from 30 to 60 minutes with rare contractions.
- ❖ Phase II (Pre burst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions.
- ❖ Phase III (Burst phase) lasts for 10 to 20 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested materials swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
- ❖ Phase IV lasts for 0 to 5 minutes and occurs between phases III and 1of 2 consecutive cycles.

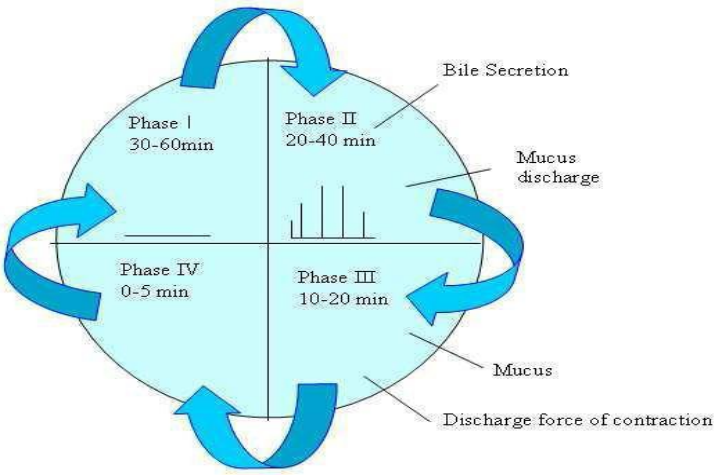


Fig.2: Motility patterns of the GIT in the fasted state

Drug candidates suitable for gastro-retention

- ✓ Drugs having poor colonic absorption but get rapidly absorbed in the upper parts of the GIT are the suitable candidates to be employed for gastro-retention.
- ✓ Drugs with narrow absorption window .e.g Levodopa and Riboflavin.
- ✓ Drugs that get primarily absorbed in stomach and upper part of stomach e.g. Cinnarizine, Chlordiazepoxide and Calcium supplements.

- ✓ Drugs having the property of degrading in stomach e.g. Metronidazole and Ranitidine
- ✓ Drugs that disturb the normal colonic bacteria e.g Amoxicillin Trihydrate
- ✓ Drugs acting locally in the stomach e.g .Antacids and Misoprostol .
- ✓ Drugs that exhibit low solubility at high ph values e.g. Diazepam, Chlorodiazepam and Verapamil HCl.

Factors affecting the Gastro retentive system[6]

The Gastric Retention Time (GRT) of dosage form is controlled by several factors that affect their efficacy as a gastro retentive system.

Density

Density of the dosage form should be less than the gastric contents (1.004 gm/ml).

Size

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm.

Shape of dosage form

Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5

Pounds per Square Inch (PSI) are reported to have better GRT. 90 % to 100 % retention at 24 hours compared with other shapes.

Single or multiple unit formulation

Multiple unit formulations show a more predictable due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

Fed or unfed state:

Under fasting conditions the GI motility is characterized by periods of strong motor activity or the MMC that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However in the fed state MMC is delayed and GRT is considerably longer.

Nature of meal

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release

Caloric content

GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

Frequency of feed

The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender

Mean ambulatory GRT in males (3.4±0.4 hours) is less compared with their age and race-matched female counter parts (4.6±1.2 hours), regardless of the weight, height and body surface.

Age

Elderly people, especially those over 70 years have a significantly longer GRT.

Posture

GRT can vary between supine and upright ambulatory states of the patient.

Disease states

Diabetes, Crohn's disease etc.,

Concomitant drug administration

Anticholinergic like Atropine and Propantheline, Opiates like Codeine and Prokinetic agents like Metoclopramide and Cisapride.

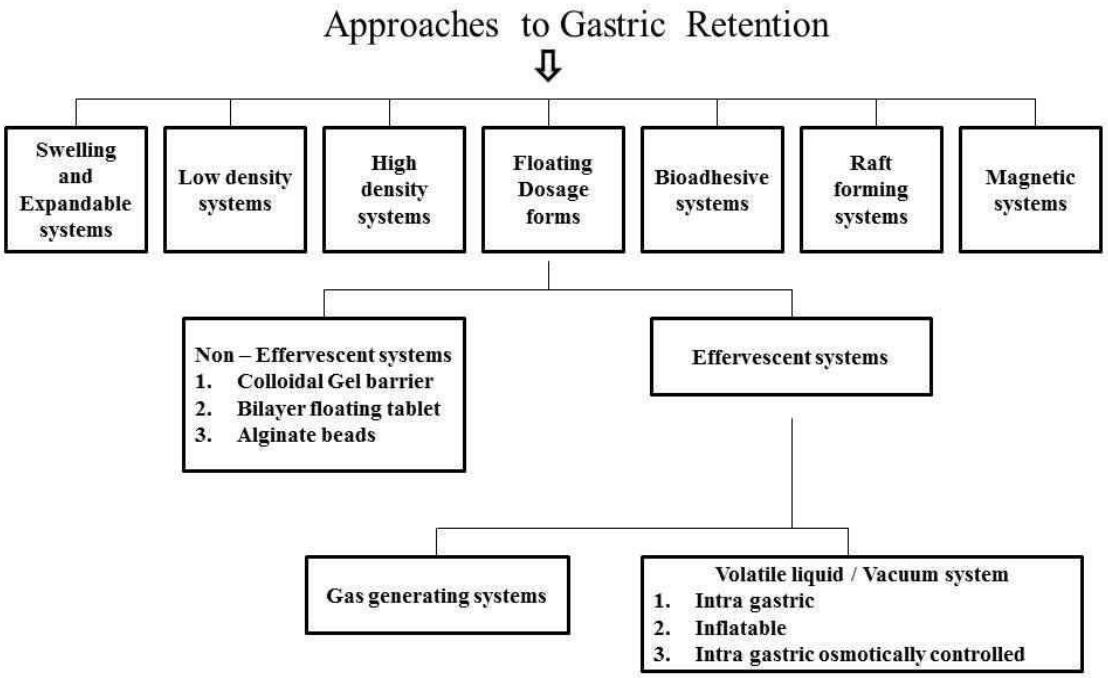


Fig. 3: Approaches to gastric retention

FLOATING DRUG DELIVERY SYSTEMS (FDDS)[7]

Floating drug delivery system or hydro dynamically balanced systems have a bulk density lower than gastric contents and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time while the system is floating on the gastric contents the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results increase in the GRT and a better control of fluctuations in plasma drug concentrations. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal.

Types of floating drug delivery system

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS.

I. Non-Effervescent FDDS

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in noneffervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids,

hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan and Carbopol.

The various types of this system are as:

1. Colloidal Gel Barrier Systems

Hydro-dynamically balanced system (HBS) of this type contains drug with gel forming or swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers. They help in prolonging the GI residence time and maximize drug reaching its absorption site in the solution form ready for absorption. These systems incorporate high levels (20 to 75 % w/w) of one or more gel forming highly swellable cellulose type hydrocolloids e.g. Hydroxy ethyl cellulose, Hydroxy propyl cellulose, Hydroxy propylmethyl cellulose, Sodium carboxy methyl cellulose incorporated either in tablets or capsules.

A. Single Layer Floating Tablets:

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid,which swells in contact with gastric fluid and maintains bulk density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as HPMC.

B. Bi-layer Floating Tablets:

A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

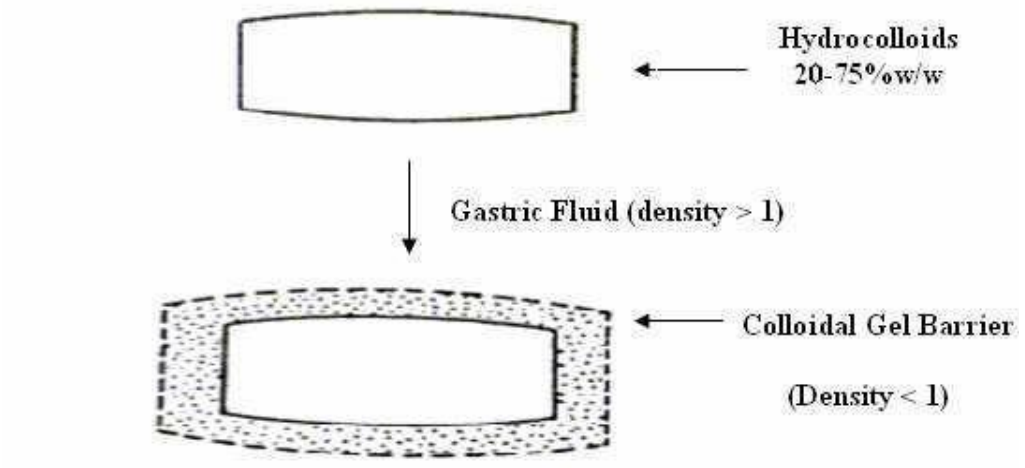


Fig. 4 :Intragastric floating tablet.

2. Micro porous compartment system

This technology is comprised of encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom surfaces. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric mucosal surface with undissolved drug. In stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the pores, dissolves the drug and carries the dissolved drug for continuous transport across the Intestine for absorption.

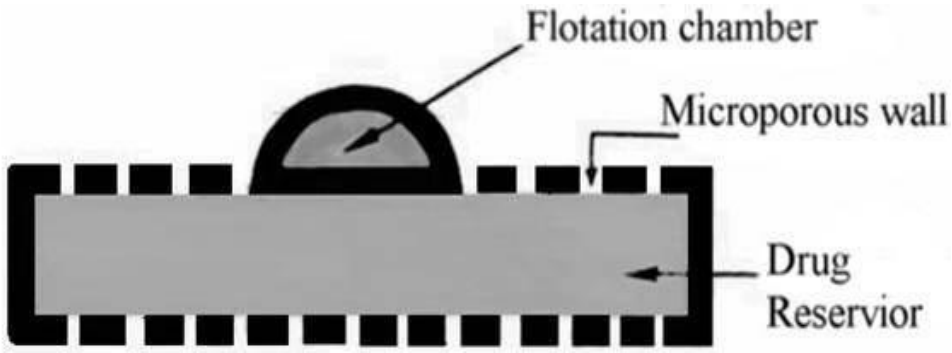


Fig. 5: Micro porous intra-gastric floating drug delivery device

3. Alginate Beads

Multi-unit floating dosage forms were developed from freeze dried calcium alginate.Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.

4. Hollow Microspheres

Hollow microspheres (Microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40 °C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer

with drug. The Micro balloons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours.

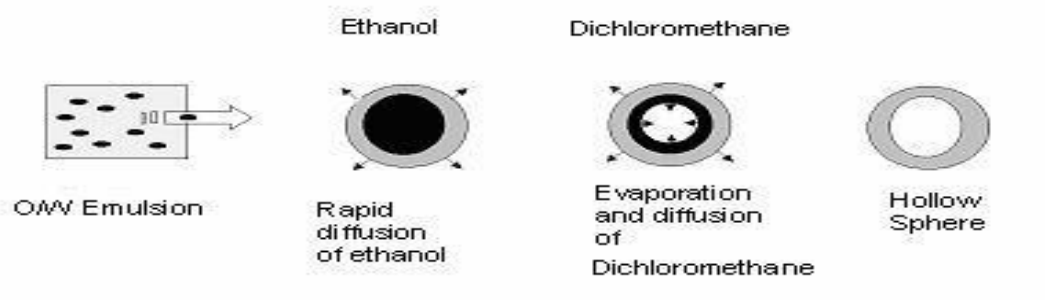


Fig.6: Mechanism of micro balloon formation by emulsion-solvent diffusion Method.

II. Effervescent FDDS[5]

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas. The gas in floatingchamber can be introduced either by volatilization of an organic solvent or by effervescentreaction between organic acids and bicarbonate salts.

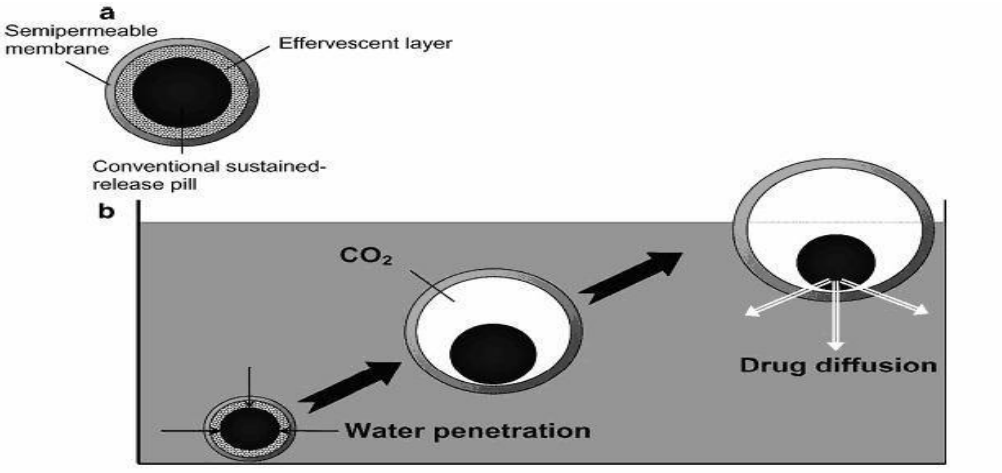


Fig.7: Floating pills: The penetration of water into effervescent layer leads to a CO_2 generation and makes the system to float.

A. Volatile liquid containing system

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of Poly vinyl alcohol, Polyethylene etc. that gradually dissolves

causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

a. Inflatable gastrointestinal delivery systems

In these systems an inflatable chamber is incorporated, which contains liquid that gasifies at body temperature to cause the chamber to inflate in the stomach. The inflatable chamber automatically inflates and retains the drug reservoir compartment in floating position. The drug continuously released from the reservoir into the gastric fluid.

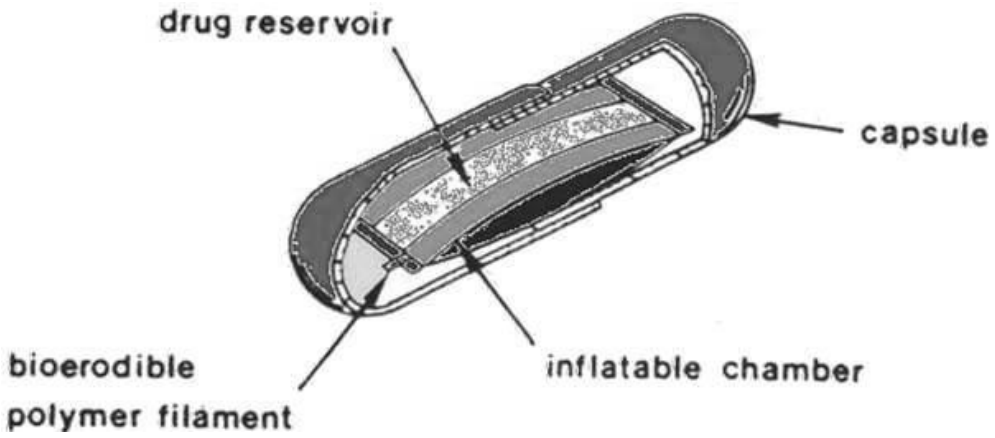


Fig.8: Inflatable gastrointestinal delivery system

b. Intragastric osmotically controlled drug delivery system

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bagand turns in forces the drug reservoir compartment to reduce its volume and activate the drug reservoir

compartment to reduce its volume and activate the drug release in solution form through the delivery orifice. The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

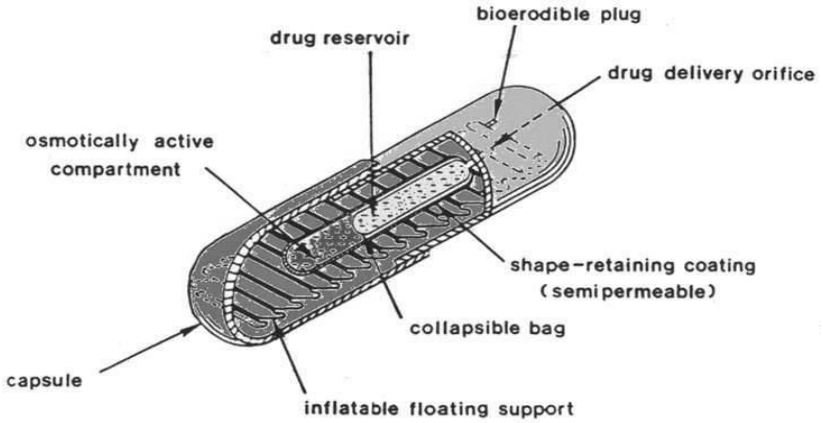


Fig.9: Intragastric osmotically controlled drug delivery system

B. Gas-generating Systems*:*

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme.

1.8. MECHANISM OF FLOATING SYSTEMS[8]

Floating drug delivery systems (FDDS) have bulk density lesser than gastric fluid , so they remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time, while the system is floating on the gastric contents the drug released slowly at the desired rate from the system as shown in Fig 9. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported. The apparatus operates by measuring continuously the force equivalent to F (as function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side as shown in fig10. This apparatus

helps in optimizing FDDS with respect to stability and durability of floating force proceed in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

$$F = F_{Buoyancy} - F_{Gravity} = (D_f - D_s)\, gv$$

Where,

F = total vertical force

D_f = fluid density

D_s =object density

V = volume

g =acceleration due to gravity

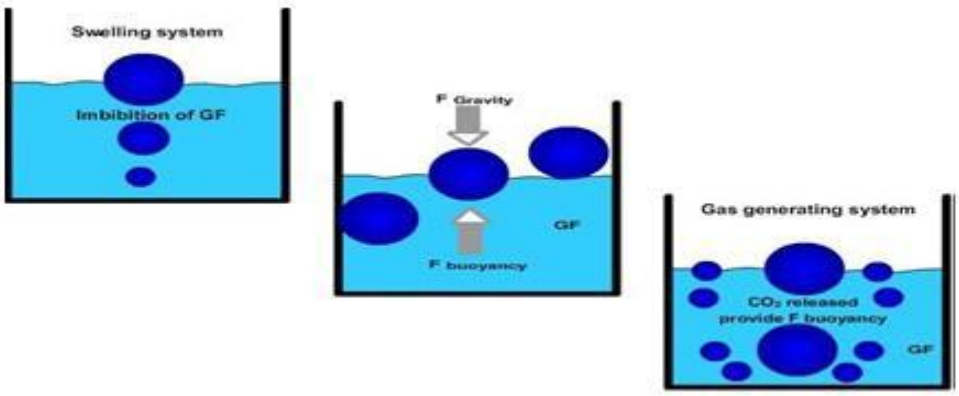


Fig.10: Mechanism of floating systems

NON-FLOATING SYSTEMS

These are another class of gastro retentive drug delivery systems which do not float but remain in the stomach for a prolonged time period14. These systems are formulated by any of the following approaches,

- **Bioadhesive systems:**

These types of systems adhere to the biological membrane (mucosa) of the stomach and maintain intimate contact with the membrane for a longer time and hence retains in stomach for its prolonged release. These systems are formulated using bioadhesive polymers which can adhere to epithelial surface in the stomach. Some of the most promising excipients that have

been used commonly in these systems include polycarbophil, carbopol, lecithins,chitosan, CMC and gliadin, etc.

- **Swelling systems:**

These are the type of non-floating gastro retentive drug delivery system which enters stomach swells (due to presence of swellable polymers) to an extent that cannot pass through the pyloric sphincter leading to its retention in the stomach.

- **High density systems:**

These systems possess density greater than the gastric fluids due to which the system sinks to the bottom and remains in the stomach. These are formulated by coating drug on heavy inert materials like zinc oxide, titanium dioxide, iron powder etc...

- **Expandable systems:**

These systems are capable of expanding and retain in the stomach for longer periods.These are usually formulated as a capsule containing dosage form in folded and compact form. After being exposed to stomach environment, capsule shell disintegrates and dosage form expands preventing its exit through the stomach. By using a suitable polymer, sustained and controlled drug delivery can be achieved.

S. Mohideen *et al.*,[9] developed a bilayer tablet consisting of Atorvastatin calcium as an immediate release layer and Metformin hydrochloride as a sustained release layer. Granules of different formulations of both the drugs were evaluated for bulk density, tapped density, compressibility index and Hausner's ratio. The prepared bilayer tablets were evaluated for weight variation, thickness, hardness, friability, drug content and *in vitro* drug release. The *in vitro* release profile showed the desired biphasic behavior. The Metformin hydrochloride released for more than 12 hrs, where as Atorvastatin calcium dissolved within 45 min.Bilayer tablet prepared from optimized formula (Trial 10) was found to be best suited method for fixed dose combination of sustained release Metformin Hydrochloride and immediate release Atorvastatin calcium.

Ajit Kulkarni and Manish Bhatia[10] prepared the regioselective bilayer floating tablets of Atenolol and Lovastatin for biphasic release profile by direct compression technique.The bilayer floating tablets comprised of two layers, immediate release layer of Lovastatin and sustained release layer of Atenolol. The immediate release layer comprised of Sodium Starch Glycolate as a super disintegrant and the sustained release layer comprised of Hydroxy Propyl Methyl Cellulose (HPMC) K100M and Xanthan gum as the release retarding polymers. Sodium bicarbonate was used as a gas generating agent. All formulation floated for more than 12 hours and release 90% of Lovastatin within 30 min. roentgenography was carried out to study the *in vivo* buoyancy of the optimized formulation and it was found to be buoyant for 8 hours in stomach.

Kotta kranthi kumar*et al.*,[11] designed the concept of bilayered tablets containing Pioglitazone hydrochloride for immediate release using cross Povidone as super disintegrant and Metformin hydrochloride for sustained release using poly ethylene oxide (PEO-303) as matrix forming polymer. The tablets were evaluated for physicochemical properties. All the values are found to be satisfactory. In vitro release studies were carried out as per USP in pH 1.2 and phosphate buffer pH 6.8 using the USP apparatus II. The release kinetics of Metformin hydrochloride was evaluated using the regression coefficient analysis. The formulated tablets (F5) shows

first order release and diffusion was the dominant mechanism of drug release. The polymer Polyethylene oxide (PEO- 303) had significant effect on the release of Metformin HCl matrix tablets (F5).Thus formulated bilayer tablets proved immediate release of Pioglitazone and Metformin HCl as sustained release over a period of 12 hours. The stability studies and FT-IR studies were also indicating the absence of strong interactions between the components and suggesting drug-excipient compatibility in all the formulations examined.

Patel Geeta M. *et al.*,[12] developed and evaluated Atorvastatin calcium (ATC) & Metoprolol succinate (MP) in same dosage form. The regioselective tablets were prepared by direct compression. Polyox WSR N-60K and HPMC K100M was used as hydrophilic polymers. Effervescent was incorporated into the formulations to float the dosage form. The amount of polymer blends was optimized using 32 full factorial design. The swellings and *in-vitro* release were studied. Floating lag time and floating duration of prepared tablets was determined. All formulations floated for more than 18-20 hrs. More than 90% of Atorvastatin calcium was released within 1 h.The stability study showed no significant change in appearance of tablets, floating characteristics and drug dissolution profile.

Dey S *et al.*,[13] formulation and evaluation of fixed-dose combination of bilayer gastroretentive matrix tablet containing atorvastatin as fast-release and atenolol assustained-release. The objective of the study was to develop bilayer tablets of atorvastatin and atenolol that are characterized by initial fast-release of atorvastatin in the stomach and comply with the release requirements of sustained-release of atenolol. Atorvastatin contained in the fast-release layer showed an initial fast-release of more than60% of its drug content within 2 hours, followed by sustained release of the atenolol for aperiod of 12 hours. It concludes that the bilayer tablets of atorvastatin and atenolol can be successfully employed for the treatment of hypertension and hypercholesterolemia together through oral administration of single tablet.

PreetiKarwa et al.,[14]designed bilayer tablet of Zolpidem Tartrate (ZT) for biphasic release and in vitro evaluation of the same. Bilayer tablets comprised two layers, i.e. immediate release and controlled release layer. The immediate release layer comprised croscarmellose sodium as a super disintegrant and the controlled release layer comprised HPMC K100M as the release retarding polymers. Direct compression method was used for formulation of the bilayer tablets. *In vitro* dissolution studies were carried out in a USP apparatus I, basket method. HPMC K100M extended the release of drug from the extended release layer for 6 hrs. FTIR studies revealed that there was no interaction between the drug and polymers used in the study. The release of Zolpidem Tartrate was found to follow a pattern of Korsmeyer-Peppas, with Quasi-Fickian diffusion. Accelerated stability studies were carried out on the prepared tablets in accordance with ICH guidelines. There were no changes observed in physicochemical properties and drug release pattern of tablets. Biphasic drug release pattern was successfully achieved through the formulation of bilayer tablets in this study.

Kulkarani *et al*.,[15] prepared the floating bilayer tablets of Diltiazem hydrochloride and Lovastatin. Direct compression technique was employed for preparing bilayer tablets.Lovastatin was formulated as immediate release layer using sodium starch glycolate as super disintegrant and diltiazem hydrochloride was formulated as sustained release layer comprising of HPMC K4M and Xanthan gum as the release retarding polymers. Sodium bicarbonate was used as a gas generating agent. All the formulations released theLovastatin within 30 minutes. HPMC K4M and Xanthan gum sustained the release for 12hours.

Prabhakar Shirse.,[16]formulated and evaluated the bilayered tablets containing Diclofenac Sodium in the sustained release (SR) portion and Ranitidine HCl in the immediate release (IR) portion in order to produce a single tablet containing two different classes of drugs.The sustained release layer of Diclofenac Sodium was prepared by using different grades of HPMC like, HPMC E15, HPMC K4M, K100M, and Ethyl Cellulose with cross carmellose along with other excipients like Magnesium stearate, Microcrystalline cellulose & PVP by wet granulation technique. The drug release study of Ranitidine HCl and Diclofenac Sodium were evaluated

using USP-XXII paddle type dissolution apparatus.The release rate of Ranitidine HCl was studied for 45 min using water as media and that of Diclofenac Sodium was studied for 2 hrs in 1.2pH buffer followed by 6 h in pH 6.8 phosphate buffer media using a developed HPLC method.

Ankarao, A *et al.*,[17] prepared the Buccoadhesive bilayer tablets of Metoprolol tartrate.Core tablet of metoprolol tartrate was prepared by direct compression technique using HPMC K4M, SCMC and Carbapol 934 as bioadhesive polymers to impart muco adhesion and ethyl cellulose to act as an impermeable backing layer. Six formulations containing the bioadhesive polymers were prepared. The formulation F2 and F5 were optimized and obeyed zero order release kinetics with non-ficikan diffusion.

Saad M. Majeed *et al.*,[18] formulated a dual therapy of peptic ulcer containing antimicrobial agent amoxicillin and anti-secretory agent esomeprazole. Different formulas of 500 mg amoxicillin were prepared as sustained release layer by wet granulation method; similarly, different formulas of 20 mg esomeprazole in form of enteric coated pellets was prepared as extended release matrix layer by direct compression technique, using pH-independent hydrophilic Eudragit polymers (E-RL100 and E-RSPM type) as matrix forming agent. The physical characteristics and release properties for compressed amoxicillin and esomeprazole matrix tablets were studied in addition the effect of polymer type, polymer concentration, polymer combination and ratio, effect of diluent type, binder type and method of preparation on the release of amoxicillin and esomeprazole from compressed matrix tablets.The results showed that formulas prepared with Hydroxy propyl methyl cellulose (HPMC K100M) and Xg in a ratio of 4:1 and PVP as binder was capable to retard the release of amoxicillin for 12 hours.

Anup Kumar Chakraborty *et al.*,[19] explained a new, simple, precise, rapid, and accurate reverse phase liquid chromatographic method for formulation containing Rosuvastatin Calcium as active pharmaceutical ingredient. A Phenomenex-C18 (250 x 4.6mm) with a particle size of 10µ column was used with a mobile phase containing a mixture of Buffer: Acetonitrile in the ratio 55:45. The flow rate was 1.0ml/min and

effluents were monitored at 244nm and eluted at 6±0.5 min. The assay was validated for the parameters like accuracy, precision, robustness and system suitability parameters.The proposed method can be useful in the routine analysis for the determination, development and to validate a new High Performance Liquid Chromatographic method (HPLC) for such an analysis.

M. Harikrishna *et al.*,[20] developed a bilayer floating tablet for Atenelol and Carvedilol using direct compression method. Bilayer floating tablets were designed to prolong gastric retention time and increase the bioavailability of the drug. Bilayer floating tablets made up of two layers, immediate release layer and controlled release layer. Immediate release layer contains sodium starch glycolate as a super disintegrating agent and controlled layer contains carbapol934p grade polymers and Ethyl cellulose as controlled release polymers .Sodium bicarbonate is used as a gas generating agent. The tablets were evaluated for physico-chemical properties such as bulk density, tapped density, hausner's ratio, hardness, thickness, friability, drug content, floating lag time, floating duration *in vitro* drug release by dissolution studies and stability studies . FT-IR studies revealed that there was no interaction between the drug and polymer used in the study. The optimized tablets B12 showed controlled and complete drug released 99.95% over a period of 24 hrs. And it follows zero order release and non-Fickian diffusion.

Sreelatha. P *et al.*,[21] developed sustained release tablets of Rosuvastatin to prolong release of time to increase in drug bioavailability.Tablets were prepared by direct compression technique using polymers HPMC K15,HPMC K50M and ethyl cellulose.Tablets were evaluated for their physical characteristics viz., hardness, thickness,friability,weight variation,drug content and floating properties. Gas generating agent plays an important role in floating lag time and drug release.The best formulation subjected for kinetic treatment.i.e. zero order, first order,pepas,Higuchi and Hixson crowell.

M.M.Gupta*et al.*,[22]designed bilayer tablets of rosuvastatin and diltiazem hydrochloride to give conventional release of rosuvastatin calcium and sustained release of diltiazem hydrochloride. The conventional release layer comprised lactose

and micro crystalline cellulose as diluents (separately and in combined form) and the sustained release layer comprised HPMC K100M and ethyl cellulose (with different ratio of HPMC K100M and ethyl cellulose) as the release retarding polymers. Direct compression method was used for formulation of the bilayer tablets. Preformulation studies were performed prior to compression. The bilayer tablets were evaluated for weight variation, dimension, hardness, friability, drug content, and disintegration time and in vitro drug release using USP dissolution apparatus type II (paddle). More than 90% of rosuvastatin calcium was released within 150 min. HPMC K100M and Ethyl cellulose sustained the release of diltiazem hydrochloride from the sustained release layer for 24 hour. After stability tests, degradation of both drugs were found but the drugs contents were found within the range.

Amish V. Panchal*et al*.,[23] established mucoadhesive buccal device of Rosuvastatin Calcium(RC) in the form of bilayered tablet. The tablets were prepared using natural gums like Xanthan gum, Tamarid gum, Gellan gum and Chitosan as bioadhesive polymers to impart mucoadhesion as well as permeation enhancement property to the formulation. Ethyl cellulose & magnesium stearate were added to act as an impermeable backing layer which gives unidirectional buccal drug delivery. Buccal devices were evaluated for different parameters such as weight uniformity, content uniformity, thickness, hardness, surface pH, swelling index, *ex vivo* mucoadhesive strength, *ex vivo* mucoadhesive time, *in vitro* drug release, and *in vitro* drug permeation. The results of study revealed that the formulation containing a combination of polymers like chitosan and natural gums shows suitatble drug permeation rate as well as mucoadhesive strength.

Mahathiyelugam*et al*.,[24] formulated and evaluated floating microspheres of carvedilol. Floating microspheres were prepared by emulsion solvent diffusion method using ethanol and dichloromethane as solvents. Ethyl cellulose and HPMC K4 M were used to prolong the release of the drug from microspheres. The prepared microspheres were subjected to various evaluatory studies. All the microspheres were found to have a size in the range of 20-40 μ and were nearly spherical in shape. Optimised batch F11 exhibited good buoyancy (73 ± 1.00 %) and sustained release (45.41 ± 0.13 % Cumulative drug dissolved) (% CDD) compared to other

formulations. It was subjected to dissolution studies using USP type 1 apparatus and Rosette rice apparatus. Drug release data was compared with the release data obtained from marketed tablet Cardivas (Controlled Release) CR. The release kinetics obtained using Rosette Rice apparatus were good compared to USP type I apparatus. The release of the drug from microspheres and Cardivas CR followed non-fickian anamolous diffusion.

A. Ankarao *et al.*,[25] established mucoadhesive buccal tablets of carvedilol in the forms of bilayered tablets. The tablets were prepared using Hydroxy propyl methyl cellulose (HPMC K4M) and sodium carboxy methylcellulose (SCMC) andCarbopol-934 (CP) as bioadhesive polymers to impart mucoadhesion and ethyl cellulose (EC) to act as an impermeable backing layer. Buccal tablets were evaluated by different parameters such as weight uniformity, content uniformity, thickness, hardness, surface pH, swelling index, ex vivo mucoadhesive strength, *in vitro* drug release, and *in vitro* drug permeation. The mechanism of drug release was found to be non-Fickian diffusion (value of n between 0.5 and 1.0) for both the buccal tablets.

M. Sujatha *et al.*,[26] formulated the Carvedilol tablets by employing Hydrophilic polymers such as HPMC K15, Xanthan gum and Guar gum, Sodium bicarbonate is used as a gas generating agent through wet granulation technique. Among the formulations F1 to F9 the F6 formulation (HPMC K15 and Gaur gum 1:1 ratio) was optimized to get 93% drug release and prolonged the drug release for more than 12hrs. The resulting formulations produced consistent hardness, uniformity in weight and low friability. The formulation with HPMC and Guar gum in the drug and polymer ratio has optimum floating lag time. The optimized formula F6 was fitted to various kinetic models and the result showed that F6 batch followed Zero order kinetics. The mechanism of drug release from F6 batch was Higuchi's with non fickian diffusion pattern. These results indicate that the selected formulation was stable during the period of accelerated stability studies.

P Gajula et al.,[27] prepared buccoadhesive tablets of Rosuvastatin calcium by direct compression method using HPMC K4M, HPMC K15M and carbopol 974P as mucoadhesive polymers and evaluated for *in vitro* drug release, *in vitro* bioadhesion,

ex vivo residence time, swelling index, surface pH and *ex vivo* drug permeation. Fifteen formulations were developed with varying concentrations of polymers. Formulations from F1 to F5 were composed of HPMC K4M, F5 to F10 using HPMC K15M and F11 to F15 using carbopol 974. The ratio of drug and polymer were varied from 1:1 to 1:5 in F1 to F10 and 1:0.25 to 1:1.50 in F11 to F15. Formulation F3 showed maximum release of the drug (97.83 ± 0.41%), and from the same formulation maximum drug has permeated (73.14 ± 0.13%) through porcine buccal membrane with a flux of 8.35 ± 0.291μg h-1cm-2, permeation coefficient of 1.34 ± 0.05 cmh-1 and maximum bioadhesive force of 24.64±0.246 respectively. FTIR results showed no evidence of interaction between the drug and polymers. The results indicate that suitable bioadhesive buccal tablets with desired permeability could be prepared.

Shinkar Dattatraya Manohar *et al.*,[28] examined the release of carvedilol from various molecular weight fractions of gelucire solid dispersions. Solid dispersions of ratios of carvedilol were prepared in different molar ratios of drug : carrier by using solvent evaporation and melting methods. The physical mixture and solid dispersion (s) were characterized for drug-carrier interaction, drug content, solubility and dissolution rate. The release rate of carvedilol from the resulting complexes was determined from dissolution studies by use of USP dissolution apparatus 2 (paddle method). The physical state and drug: gelucire interaction of solid dispersions and physical mixtures were characterized by X-ray diffraction (XRD), Infra Red Spectroscopy (IR) and Differential Scanning Calorimetry (DSC). The dissolution rate of carvedilol was increased significantly in all of the solid dispersion systems compared to that of the pure drug and physical mixtures. The solid dispersion prepared in the molar ratio of 1:2 by the solvent evaporation method was found to have the fastest dissolution profile.

Omar s. salih*et al.*,[29] formulated and evaluated Rosuvastatin calcium niosomes using non-ionic surfactants (Span 20,Span 60,span 80), cholesterol and lecithin in different ratios by film hydration method and evaluate the formulas in terms of assay of drug in each formula (entrapment efficiency) by HPLC, particle size, morphology, *in-vitro* drug release and ex-vivo permeation study. Scanning electron microscopy

(SEM) and transmission electron microscopy (TEM) were used for characterization of the selected formula. Fourier transform infrared (FTIR) was used for study of drug – excipients compatibilities. All formulas gave obvious morphology in the presence of cholesterol as a stabilizing agent, formula with span 60 had more entrapment efficiency than all other formulas, with slower release after 7 hours *in vitro* dissolution media, TEM results show vesicle size of F6 niosomal vesicle was 150nm in diameter.

Sowjanya Polanki *et al.*,[30] developed oral gastroretentive floating tablets of carvedilol, to prolong the gastric residence time and improves the bioavailability of the drug as well as its half life. All the precompression parameters of formulation blends of Carvedilol floating matrix tablets were evaluated for Angle of repose, Bulkdensity, Tapped density, Compressibility index and Hausner's ratio.All the values were within the limit as per U.S.P. The best floatingperformance and the best *in vitro* drug release profile were achieved byformulation F4 which contains Drug: xanthan gum: karaya gum in aratio of 1:0.5:0.5 gave the drug release (99.64%) up to 24 h.

Ramnath Y.Lahare*et al.*,[31] developed three new simple, economic spectrophotometric methods for quantitative estimation of Rosuvastatin Calcium in bulk formulation. First method includes determination of Rosuvastatin Calcium at absorption maxima 252 nm, second method applied was area under curve for analysis of Rosuvastatin Calcium in the wavelength range of 247-257 nm and third method was first order derivative. Beer law obeyed in the concentration range of 5-35 μg/ml for all three methods. The correlation coefficients were found to be 0.974, 0.982 and 0.982by absorption maxima, area under curve and first order derivative spectra. Results of analysis were validated statistically and by performing recovery studies. The mean percent recoveries were found satisfactory for all three methods. The percentage label claim was found in the range of 100.48% to 101.05%.

Venkata srikanth meka *et al.*,[32] enhanced the solubility of carvedilol phosphate and formulated it into non-effervescent floating tablets using swellable polymers. Solid dispersions (SD) of carvedilol were prepared with hydrophilic carriers such as

polyvinyl pyrrolidone and poloxamer to enhance solubility. Non-effervescent floating tablets were prepared with a combination of optimized solid dispersions and release retarding polymers/swellable polymers such as xanthan gum and polyethylene oxide. Tablets were evaluated for physicochemical properties such as hardness, thickness and buoyancy. SD prepared with the drug to poloxamer ratio of 1:4 by melt granulation showed a higher dissolution rate than all other dispersions. Formulations containing 40 mg of polyethylene oxide (C-P40) and 50 mg xanthan gum (C-X50) were found to be best, with the drug retardation up to 12 hours. Optimized formulations were characterized using FTIR and DSC and no drug and excipient interactions were detected.

Nagesh C *et al.*,[33] developed floating tablets of carvedilol using HPMC and various natural gums like guar gum and xanthan gum and gum ghatti along with incorporation of gas generating agent, sodium bicarbonate.The floating tablet of carvedilol was prepared by wet granulation technique using solution of PVP K30 in isopropyl alcohol, using varying concentration of HPMC and natural gums.Post compressional parameters like hardness,thickness,friability,weightvariation,contentuniformity,in vitro buoyancy and in vitro dissolution studies were carried out. The results of in vitro release of floating tablets containing natural gums has shown maximum drug release upto 97% in 24 hrs and remain buoyant for 24 hrs.

BurraShashidher*et al.*,[34] made an attempt to enhance the dissolution profile, absorption efficiency and bioavailability of water insoluble drugs, such as Carvedilol. A novel "Powder Solution Technology" involves absorption and adsorption efficiency, which makes use of liquid medications, admixed with suitable carriers, coating materials and formulated into a free flowing, dry looking, non adherent and compressible powder forms. Based upon a new mathematical model expression, improved flow characteristics and hardness of the formulation have been achieved by changing the proportion of Avicel ® PH 200 and Aerosil ® PH 200 from 20:1 ratio to 5:1. Higher dissolution rates (90-99.9%) were observed in all liquisolid formulations, when compared with a conventional marketed product (CARCA®12.5 mg) within twenty minutes.

Rohit B Mane *et al*.,[35] prepared and evaluated of carvedilol microsphere using spray drying technique and to optimize the spray drying parameters to get the optimum formulation. The carvedilol microsphere were prepared by spray drying technique using ethyl cellulose and PEG 6000 as sustained release polymers. Nine batches were prepared by using ethyl cellulose and PEG 6000 in different polymer ratios and prepared microspheres were evaluated for the particle size, percentage drug entrapment and percentage drug release. Experimental designs were built to investigate the effects of five parameters on production yields and particle size of spray-dried microspheres of carvedilol. These factors concerned aspiration speed, flow rate, drug polymer ratio, temperature difference between inlet temperature and outlet temperature. Three formulations containing ethyl cellulose, PEG 6000 and carvedilol were tested. The aim of the study was to optimize the operating conditions to maximize production yields while minimizing the particle size.

PisipatiAparna*et al*.,[36] developed and optimized carvedilol transdermal delivery system.Solvent casting method was used to prepare patches using polymethyl methacrylate (PMMA) and Eudragit E100 (EE100) polymers, dimethyl sulfoxide (DMSO) penetration enhancer, dibutyl phthalate (DBP) plasticizer and Tween 80 surfactant. A 2^3 factorial design was used based on three variables (PMMA, EE100, DMSO) at two levels Second order polynomial equations indicating interplay of ingredients were obtained by factorial design using SigmaTech software for 1, 4, 8 and 20 h release data. so the design was extended to central composite design (CCD). The target formulation was obtained from contour plots and evaluated for various physicochemical parameters including *in-vitro* dissolution studies.

BK Garg*et al*.,[37] developed and evaluated a pulsatile drug delivery system consisting of cores coated with two layers of swelling and rupturable coatings was prepared and evaluated as pulsatile drug delivery system. Cores containing Rosuvastatin calcium as model drug were prepared by direct compression of different ratios of spray-dried lactose and microcrystalline cellulose and were then coated sequentially with an inner swelling layer containing a super disintegrant (croscarmellose sodium) and an outer rupturable layer of ethylcellulose. The effect of level of swelling layer was investigated. Rupture and dissolution tests were performed

using the USP XXIV paddle method at 50 rpm in 0.1 N HCl. The lag time of the pulsatile release tablets decreased with increasing levels of swelling layer. Increasing levels of the ethylcellulose coating retarded the water uptake and thus prolonged the lag time.

P. Rohini *et al* .,[38] designed a formulation of orally disintegrating tablets of Rosuvastatin. Orally disintegrating tablets of Rosuvastatin were formulated by Super disintegrant addition method by direct compression technique. All the fourteen formulations were evaluated for disintegration time, hardness and friability, this Super disintegrant addition method exhibits the lowest disintegration time, hence it is ranked as the best among the methods. Further fourteen batches were prepared by using sodium starch glycolate, croscaramellose sodium, Lycoat Rs720 and cross povidone in different concentrations. All the formulations were evaluated for weight variation, hardness, friability, drug content, *in-vitro* disintegration time, wetting time, *in-vitro* dissolution study. Among all the formulations F13 (containing crosspovidone and sodium starch glycolate (1:1) (8%)) was considered to be the best formulation, which release up to 97% of the drug in 5 mins. A comparison of *In vitro* drug release was made with marketed product of Rosuvastatin which shows 93% drug release in 1 hour.

Dhiren S. Patel *et al.*[39] developed a versatile, accurate, precise and economic method for simultaneous determination of Rosuvastatin calcium and Aspirin in fixed dose combination products. The absorbance values at 242.0 nm and 297.0 nm and 287.5nm (isoabsorptive point) were used for the estimation of Rosuvastatin calcium and Aspirin, respectively without mutual interference. This method obeyed Beer's law in the concentration range of 2–26 μg /ml for Rosuvastatin calcium and 5-25 μg /ml for Aspirin. The results of analysIs have been validated statistically for linearity, accuracy and precision, LOD and LOQ of the proposed method.

Syed Zia Ul Quasim*et al.*,[40] prepared a floating drug delivery system for the model drug Rosuvastatin calcium, and evaluating the various processing parameters including the buoyancy studies and *in vitro* drug release studies. Four formulations containing varying proportions of polymers like HPMC K4M and Ethyl cellulose and

fixed amount of gas generating agent such as Sodium bi carbonate and hydrophobic meltable material like bees wax were prepared. The tablets were prepared by melt granulation technique and the prepared tablets remained buoyant for more than 8hrs in the release medium. The proportions of the polymers showed significant difference in the release of the drug. All the formulations exhibited diffusion dominant drug release and were found to be stable.

Chaudhari BG *et al.*,[41] developed a simple and economical dual wavelength spectrophotometric method for the simultaneous estimation of rosuvastatin and diltiazem in their combined dosage forms. The method was based on property of addivity of absorbances. At 295.6 rosuvastatin showed absorbance but diltiazem showed zero absorbance. The two wavelengths on rosuvastatin curve were found out where it showed same absorbance, which were 227 and 247.4 nm. Diltiazem showed adequate absorbances at these wavelengths. The method involved solving of an equation based on measurement of absorbances at three wavelengths 295.6, 227, and 247.4 nm. The proposed method was found to be simple, economical, accurate, and reproducible for routine analysis of both drugs in tablet dosage forms.

BheemeswaraRao K *et al.*,[42] developed the immediate release film coated formulation of Rosuvastatin Calcium to improve the distribution of Rosuvastatin calcium, improve the product stability.The immediate release formulation of Rosuvastatin Calcium was prepared by wet granulation method and by using fluidized bed coating method. Different formulations were made by using various concentrations of super disintegrant Poly plasdone XL-10 and granulating fluids like water, iso propyl alcohol (IPA) and Butyl hydoxytuolene (BHT). Opadry pink 03k540019 was used as film coating mateial .The Prepared formulations were evaluated for the physical characteristics, *invitro* dissolution and stability at 40°C/ 75% RH for three months. The formuation (F8) of film coated rosuvastatin calcium tablets showed best release profile.

A. Ramu*et al.*,[43] made a new attempt to enhance the solubility, dissolution rate and oral bioavailability of poorly soluble rosuvastatin by formulating it as solid dispersions using various techniques with polyethylene glycol (PEG) 6000 as a

carrier. Fast dissolving tablets of rosuvastatin were prepared with super disintegrants like sodium starch glycolate,croscarmellose sodium, pregelatinized starch and mannitol from the optimized solid dispersions. Tablets were evaluated for physical parameters and drug release by *in vitro* dissolution studies. Surface characteristics, drug-excipient interactions and crystal morphology of optimized solid dispersions were evaluated by SEM analysis, DSC and XRD studies, respectively.

Ehsan ali Mohamed *et al.*,[44] developed oro dispersible tablets of Rosuvastatin using different types of super disintegrants to enhance the disintegration and dissolution of Rosuvastatin to improve bioavailability of the drug. Many trials were made to prepare a satisfactory rosuvastatin orodispersible tablet using direct compression and wet granulation method. Prepared tablets were evaluated for various parameters like weight variation, hardness, friability, wetting time, in vitro disintegration time, drug content, water absorption ratio and *in vitro* drug release. Formulas prepared by direct compression showed good flowability, while formulas prepared by wet granulation showed very poor flow properties. Various super disintegrants were used including croscarmellose (CCS), sodium starch glycolate (SSG) and crospovidone (CP), the latter found to be the best in term of showing the fastest disintegration time.

GV.Wadageri *et al.*,[45]made an attempt to design and evaluate buccoadhesive bilayer tablets of carvedilol (beta blocker), in order to overcome bioavailability problems, to reduce dose dependent side effects and frequency of administration. Bilayer buccal tablets of carvedilol were prepared by direct compression method using combination of polymers (such as hydroxypropyl methylcellulose 15 cps, 50 cps and K4M along with Carbopol 934p and ethyl cellulose as backing layer. Fifteen formulations were developed with varying concentrations of polymers. The designed tablets were evaluated for various physical and biological parameters like drug content uniformity, *in vitro* drug release, short-term stability. Among the 15 formulations, the formulation F151 containing hydroxypropyl methylcellulose 15 cps (48% w/w of matrix layer), Carbopol 934p (2% w/w of matrix layer) and mannitol (channeling agent, 34.5% w/w of matrix layer) was found to be promising.

Y.Nirupa rani *et al.*,[46] developed and validated simple, sensitive and specific spectrophotometric method for the determination of Carvedilol, an alpha adrenergic

receptor blocker, anti hypertensive drug in pure form and in pharmaceutical formulations by UV visible spectroscopic methods. The developed method was validated with respect to linearity, accuracy, precision and specificity. The adequate drug solubility and maximum sensitivity was found in chloroform. The λmax or the absorption maxima of the drug was found to be 286 nm. The calibration range was studied from 50% -150% and correlation was found to be R2 = 0.998 which was within the limits of ICH guidelines. They analyzed and evaluated an analytical method and compared with validation report generated for the developed method. No interference was found from excipients at the selected wavelength and analysis conditions.

Anandakumar Karunakaran*et al*.,[47] described two methods for the simultaneous estimation of Rosuvastatin Calcium and Fenofibrate in binary mixture. The first method was based on UV Spectrophotometric determination of two drugs, using simultaneous equation method. It involves absorbance measurement at 243nm (λmax of Rosuvastatin Calcium) and 287nm (λmax of Fenofibrate) in methanol; linearity was obtained in the range of 1-6 µg/ml and 4-28 µg/ml for Rosuvastatin Calcium and Fenofibrate, respectively. The second method was based on HPLC separation of two drugs in reverse phase mode using Luna C18 column. Linearity was obtained in the concentration of 1-7 µg/ml and 4-28 µg/ml for Rosuvastatin Calcium and Fenofibrate, respectively. Both these methods have been successively applied to pharmaceutical formulation and were validated according to ICH guidelines.

AIM OF THE WORK

- To combine Rosuvastatin calcium and Carvedilol in a single dosage form due to their cardioprotective effects on various cardiovascular events.
- To increase the gastric residence time of formulation in order to increase the bioavailability and efficacy of drug for better patient compliance by giving in floating drug delivery system.
- To optimize the immediate release tablet of Rosuvastatin Calcium by direct compression method using various super disintegrants such as Sodium Starch Glycolate, Crospovidone and Croscarmellose Sodium.
- To optimize the gastroretentive floating layer tablets of Carvedilol by Direct compression method using natural and synthetic polymer such as Xanthan gum, guar gum and HPMC K 100 in different ratios.
- To formulate and evaluate the gastroretentive bilayer floating tablets from the optimized batches of immediate and floating tablet formulations.

PLAN OF WORK

- Preformulation studies.
    - Raw material analysis
    - Physical and chemical compatibility studies
- Construction of Calibration curve.
- Precompression studies of drug and blends.
    - Bulk density
    - Tapped density
    - Angle of repose
    - Carr's index
    - Hausner's ratio
- Formulation of immediate release (IR) compressed tablets.
- Post compression studies of IR tablets for physical parameters like
    - Physical appearance
    - Uniformity of weight
    - Hardness, thickness, diameter
    - Friability
    - Determination of drug content of tablets

- Disintegration studies of IR tablets.
- *In-vitro* dissolution studies of IR tablets.

❖ Formulation of Floating tablets.

❖ Post compression studies of Floating tablets for physical parameters like

- Physical appearance
- Hardness, Thickness, Diameter and Friability
- Determination of drug content of floating tablets
- Uniformity of weight
- Evaluation of floating characteristics of floating tablets- Buoyancy test.

❖ *In-vitro* dissolution studies of floating tablets.

❖ Formulation of Bilayer Floating Tablets (BFT).

❖ Post compression studies of bilayer floating tablets like

- Uniformity of weight
- Hardness, thickness, diameter and friability
- Determination of drug content

❖ Evaluation of floating characteristics of bilayer floating tablets

❖ *In-vitro* dissolution studies of bilayer Floating tablets.

❖ Evaluation of release kinetics of BFT.

❖ Stability studies of prepared tablets as per ICH guidelines

RATIONALE FOR COMBINING ROSUVASTATIN CALCIUM AND CARVEDILOL IN GASTRO RETENTIVE DRUG DELIVERY:[48,49,50]

- Cardiovascular diseases are one of the life threatening diseases of the world. It mainly includes arteriosclerosis, coronary artery disease i.e. angina pectoris, myocardial infarction, congestive cardiac failure, cardiac arrhythmias, angina pectoris, hypertension, hyperlipidemia etc.
- Hypertension and dyslipidemia are conditions that can coexist frequently. National Health and Nutrition Examination Survey (NHANES III) has shown that 64% of patients with hypertension also have dyslipidemia and conversely, approximately 47% of patients with dyslipidemia have hypertension.
- Rosuvastatin Calcium and Carvedilol are often prescribed simultaneously in cardiac prescriptions. More of cardiac events can be prevented when these drugs are given in combination. So it could be an appropriate cardio protective formulation with the treatment of Hyperlipidemia and Hypertension.
- And the gastroretentive drug delivery system is one in which the gastroretentive dosage form releases the drug over an extended period in the stomach and upper GIT thus, enhancing the opportunity of absorption. Both the drugs have narrow absorption window in the upper GIT and they are suitable for gastro retentive drug delivery.

RATIONALE FOR SELECTION OF ROSUVASTATIN CALCIUM OVER OTHER STATINS[50]:

- ✓ Rosuvastatin Calcium is a currently used anti-hyperlipidemicagent.It is a first line drug for coronary artery disease.
- ✓ It is a selective and competitive inhibitor ofHMG-CoA reductase.
- ✓ It is the most effective statin at reducing LDL-C,triglycerides and total cholesterol.
- ✓ It reduces 40 – 70 % LDL level.
- ✓ The half life of Rosuvastatin Calcium is 19 hrs. So it is suitable for immediate release formulation.

RATIONALE FOR SELECTION OF CARVEDILOL OVER TRADITIONAL BETA BLOCKERS[51]

- ✓ Carvedilol is a nonselectiveβ-adrenergic blocking agent with α1-blocking activity prescribed for the treatment of angina, hypertension and congestive heart failure.
- ✓ Traditional beta blockers have been shown to facilitate weight gain and increase triglycerides.
- ✓ Carvedilol has been found to have a neutral effect on weight and triglycerides. So it is the better choice compared to traditional beta blockers in the high risk cardiac patients with hyperlipidemia.

DYSLIPIDEMIA[52,53]

DEFINITION:

Dyslipidemia is an abnormal amount of lipids (cholesterol and / or fat) in the blood. In developed countries, most dyslipidemias are hyperlipidemias; that is an elevation of lipids in the blood. This is often due to diet and lifestyle. Prolonged elevation of insulin levels canal so lead to dyslipidemia. Likewise, increased levels of O-Glc NA transferase (OGT) may cause dyslipidemia.

HYPERLIPIDEMIA

The lipids of human plasma are transported in macromolecular complexes termed lipoproteins. A number of metabolic disorders that involve elevations in levels of any of the lipoprotein species are thus termed hyper lipoproteinemias or hyperlipidemias. Term hyperlipidemia denotes increased levels of triglycerides in plasma. Hyperlipidemia is a major cause of atherosclerosis and atherosclerosis-associated conditions such as coronary heart disease (CHD), ischemic cerebro vascular disease and peripheral vascular disease.

Hyperlipidemia (elevated levels of triglycerides or cholesterol) and a reduced HDL-C level occurs as a consequence of several interrelated factors that affect the concentrations of the various plasma lipoproteins. These factors may be lifestyle or behavioural (diet or exercise), genetic (mutations in gene regulating lipoprotein levels) or metabolic (diabetes mellitus) or other conditions that influence plasma lipoprotein metabolism.

Lipoprotein transport in the blood

Lipids and cholesterol are transported through the blood as macromolecular complexes of lipid and protein known as lipoproteins. These consist of a central core of hydrophobic lipid (triglycerides and cholestryl esters) encased in a more hydrophilic coat of polar substances- phospholipids, free cholesterol and associated apolipoproteins. There are four main classes of lipoproteins differing in relative proportion of the core lipids and in the type of apoprotein. They differ on the basis of their size and density.

They are classified into:

1. High density lipoproteins (HDL)
2. Low density lipoproteins (LDL)

3. Very Low density lipoproteins (VLDL)

4. Chylomicrons

Each of this lipoprotein classes has a specific role in lipid transport in the circulation and there are different pathways for exogenous and endogenous lipids. In the exogenous pathway cholesterol and triglycerides are absorbed from the gastrointestinal tract and transported in the lymph and then in the plasma as chylomicrons (diameter 100-1000 nm) to muscle and adipose tissue. Here the cores of chylomicrons are hydrolyzed by lipoprotein lipase and the tissues take up the resulting free fatty acids. The chylomicron remnants (30-50receptors on hepatocytes and undergo endocytosis. Cholesterol is liberated within the liver cell and may be stored, oxidized to bile acids or secreted in the bile unaltered. Alternatively, it may enter the endogenous pathway of lipid transport in VLDL. In the endogenous pathway cholesterol and newly synthesized triglycerides are transported from the liver as VLDL (30-80nm) to muscle and adipose tissues where the triglycerides are hydrolyzed and the resulting fatty acids enter the tissues. During this process the lipoprotein particles become smaller (20-30nm) but still have a full complement of cholesteryl esters and ultimately become LDL, which provides the source of cholesterol for incorporation into cell membranes and for synthesis of steroids and bile acid.

ETIOLOGY:

Primary and secondary causes contribute to dyslipidemia.

PRIMARY CAUSES

Primary causes are single and multiple gene mutations that result in either overproduction or defective clearance of TG and LDL cholesterol or in under production or excessive clearance of HDL.

SECONDARY CAUSES:

Secondary causes contribute to most cases of dyslipidemia in adults. The most important secondary cause in developed countries is a sedentary lifestyle with excessive dietary intake of saturated fat, cholesterol and transfats. Diabetes is an especially significant secondary cause because patients tend to have anatherogenic combination of high TGs; high small, dense LDL fractions; and low HDL(diabetic dyslipidemia). Patients with type 2 diabetes are especially at risk.

SIGNS AND SYMPTOMS:

- Dyslipidemia itself usually causes no symptoms but can lead to symptomatic vascular diseases including coronary artery disease (CAD) and peripheral arterial disease.
- High levels of TGs (>1000mg/dL) can cause acute pancreatitis.
- High levels of LDL can cause eyelid xanthelasmas; arcuscorneae; and tendinous xanthomas at the Achilles, elbow and knee tendons and over meta carpophalangeal joints.
- Severe hyper tri glyceridemia (>2000mg/dL) can give retinal arteries a creamy white appearance (lipemiaretinalis).
- Extremely high lipid levels give a lactescent (milky) appearance to plasma.
- Symptoms include Parasthesias, Dyspnea and Confusion.

SCREENING:

A Fasting lipid profile (TC, TG, HDL-C, LDL-C) should be obtained in all adults ≥20 years and should be repeated every five years.

MANAGEMENT:

The main goal of dyslipidemia management is to maintain blood cholesterol level within the normal range as possible.

- Lifestyle modification focusing on the reduction of saturated fat and cholesterol intake.
- Weight loss.
- Increased physical activity.
- Smoking cessation

TREATMENT:

DRUGS- FOUR CLASSES OF LIPID LOWERING DRUGS ARE

- **HMG-CoA reductase inhibitors (Statins):**

  Lovastatin, simvastatin, pravastatin, atorvastin, rosuvastin.

- **Bile acid sequestrants (Resins):**Cholestyramine, colestipol.
- **Activate lipoprotein lipase (Fibric acid derivatives):**
  Clofibrate, gemfibrozil, benzafibrate, and fenofibrate.
- **Inhibit lipolysis and triglyceride synthesis:** Nicotinic acid

HYPERTENSION[54,55,56]

Blood is carried from the heart to all parts of the body in blood vessels. Each time the heart beats, it pumps blood into the vessels. Blood pressure is created by the force of blood pushing against the walls of blood vessels (arteries) as it is pumped by the heart. Hypertension, also known as high or raised blood pressure, is a condition in which the blood vessels have persistently raised pressure. The higher the pressure in blood vessels the harder the heart has to work in order to pump blood. If left uncontrolled, hyper tension can lead to a heart attack, an enlargement of the heart and eventually heart failure. Hypertension can also lead to kidney failure, blindness, rupture of blood vessels and cognitive impairment.

Blood pressure is measured in millimeters of mercury (mm Hg) and is recorded as two numbers usually written one above the other. The upper number is the systolic blood pressure the highest pressure in blood vessels and happens when the heart contracts, or beats. The lower number is the diastolic blood pressure- the lowest pressure in blood vessels in between heart beats when the heart muscle relaxes. Normal adult blood pressure is defined as a systolic blood pressure of 120 mmHg and a diastolic blood pressure of 80 mmHg.

Table 1: Classification of hypertension

Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Optimal	<120	<80
Normal	120–129	80–84
High normal	130–139	85–89
Grade 1 hypertension	140–159	90–99
Grade 2 hypertension	160–179	100–109
Grade 3 hypertension	≥180	≥110

Etiology:

Hypertension is either due to some cause or without identifiable cause. There are two types of hypertension.

1. Primary hypertension
2. Secondary hypertension

Primary hypertension:

Primary (essential) hypertension is the most common form of hypertension, accounting for 90–95% of all cases of hypertension. In almost all contemporary societies, blood pressure rises with aging and the risk of becoming hypertensive in later life is considerable. Hypertension results from a complex interaction of genes and environmental factors.

Genetic factors:

The role of heredity in the etiology of essential hypertension has long suspected; e.g. occurrences of hypertension in twins.

Racial and environmental factors:

During a survey in US, it was revealed that the incidence of hypertension in black is more than whites. Environmental factors like salt intake, obesity has influence on the hypertension.

Pathophysiology:

Hypertension is a risk factor for atherosclerosis and cardiovascular complications like myocardial infarction, angina pectoris, and congestive cardiac failure, whether the cause of hypertension is known or unknown. In secondary hypertension, in less than 10% cases causes of hypertension are understood whereas in more than 90% cases, the mechanism of essential hypertension remains largely obscure. In general, two hemodynamic forces viz-cardiac output and peripheral resistance regulate the normal blood pressure. The role of kidney particularly in secondary hypertension by elaboration of rennin and subsequent formation of angiotensin II is well established. Chronic hypertension results in damage to end organs like eyes, brain, kidneys and heart. It is possible to correlate the duration of hypertension by considering the severity of end organ damage.

Secondary Hypertension:

It is secondary to some other underlying disease. When the actual cause is treated hypertension comes to normal.

Underlying causes may be as follow:

1. Rennin angiotensin mediated hypertension.
2. Endocrine disorders

There are following types of hypertension:

Renal hypertension:

Renal diseases like renal vascular hypertension produce renal hypertension, which is associated with the renal artery. Renal hypertension may be produced by any one of three interrelated mechanisms

a) Activation of renin-angiotensin system.

b) Sodium and water retention.

c) Decreased release of vasodepressor materials.

Endocrine hypertension:

A number of hormonal secretions may produce secondary hypertension like adrenal glands, parathyroid glands, and oral contraceptives. Usually, hypersecretion of tumour of endocrine glands; e.g. Cushing's syndrome, primary hyper aldosteronism, pheochromocytoma, oral contraceptives, and use may lead to release of angiotensin I.

Neurogenic:

Psychogenic polyneuritis, increased intracranial hypertension and secretion of spinal cord are the uncommon causes of secondary hypertension.

Contraction of aorta:

Causes secondary hypertension in the upper part of the body due to constriction. Diastolic hypertension results from changes in circulation.

Causes of hypertension

Behavioral risk factors:

There are many behavioral risk factors for the development of hypertension including:

- Consumption of food containing too much salt and fat, and not eating enough fruit and vegetables
- Harmful levels of alcohol use
- Physical inactivity and lack of exercise
- Poor stress management.

Socioeconomic factors:

Social determinants of health, e.g. income, education and housing, have an adverse impact on behavioral risk factors and in this way influence the development of hypertension.

Other factors:

In some cases there is no known specific cause for hypertension. Genetic factors may play a role, and when hypertension develops in people below the age of 40 years, it is important to exclude a secondary cause such as kidney disease, endocrine disease and malformations of blood vessels. Preeclampsia is hypertension that occurs in some women during pregnancy. It usually resolves after the birth but it can sometimes linger, and women who experience preeclampsia are more likely to have hypertension in later life.

Symptoms of high blood pressure

There is a common misconception that people with hypertension always experience symptoms, but the reality is that most hypertensive people have no symptoms at all. Sometimes hypertension causes symptoms such as,

- headache,
- shortness of breath,
- dizziness,
- chest pain,
- palpitations of the heart and
- nose bleeds.

It can be dangerous to ignore such symptoms, but neither can they be relied upon to signify hypertension. Hypertension is a serious warning sign that significant lifestyle changes are required. The condition can be a silent killer and it is important for everybody to know their blood pressure reading.

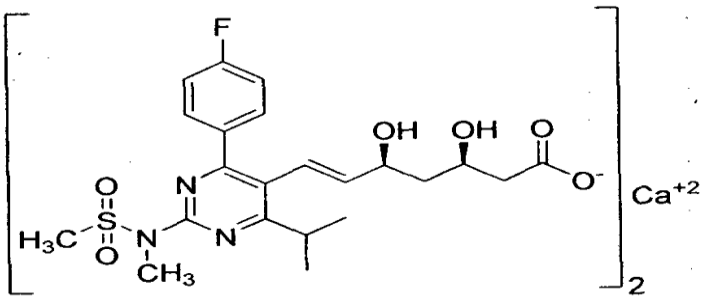
Treatment

- Diuretics
- Angiotensin converting enzymes (ACE) inhibitors
- Alpha adrenergic receptor blockers
- Beta adrenergic receptor blockers
- Calcium channel blockers
- Central adrenergic inhibitors
- Vasodilators
- Lifestyle modification to reduce risk factors

ROSUVASTATIN CALCIUM[58,59,60]

Rosuvastatin calcium is a synthetic lipid lowering agent which is an inhibitor of 3-hydroxy-3-Methylglutaryl-coenzyme A (HMG-Co-A) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Chemical structure:



Chemical Name: Bis[(E)-7-[4-(flurophenyl)-6-isopropyl-2- [methyl (methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3-5-dihydroxyhept-6-enoic acid] calcium salt

Molecular formula:$(C_{22}H_{27}FN_3O_6S)_2Ca$

Molecular weight:1001.14

Melting point: 151-156ºC

Dosage and administration:5 to 40 mg per day orally

Description : An off white to creamish white crystalline powder

Solubility : Soluble in methanol and Dimethyl sulphoxide, practically insoluble in water.

Mechanism of Action:

Rosuvastatin is a selective and competitive inhibitor of HMG-Co-A reductase, the rate-limiting enzyme that converts -3-hydroxy-3- methyl glutaryl coenzyme A to mevalonate, a precursor of cholesterol.

Table 2.Effect of drugs on LDL and HDL levels

Treatment	LDL- C reduction	HDL- C increase
Atorvastatin (10-80 mg)	37-51 %	5.7-2 %
Simvastatin (10-80 mg)	28-46 %	5.3 -6.8 %
Rosuvastatin (10-40 mg)	**46-55 %**	**7.6-9.6 %**
Pravastatin (10-40 mg)	20-30 %	3.2-5.5 %

Pharmacokinetics

Absorption:

Absolute bioavailability is 20 %. The half-life is 19 hrs and does not increase with increasing dose. Significant LDL-C reductions are seen when rosuvastatin is given with or without food, and not considering time of day of drug administration.

Distribution:

Volume of distribution of rosuvastatin at steady state is approximately 134 litres. Rosuvastatin is approximately 90% bound to plasma proteins, mostly albumin.

Metabolism:

Rosuvastatin is not extensively metabolised; about 10% of a radio labelled dose is recovered as metabolite.

Excretion:

Rosuvastatin undergoes limited metabolism (approximately 10%), mainly to the N- desmethylform, and 90% is eliminated as unchanged drug in the faeces with the remainder being excreted in the urine. The elimination half-life ($t_{1/2}$) of rosuvastatin is approximately 19 hrs.

Drug-Drug Interactions

Ketoconazole, Erythromycin, Cyclosporine, Warfarin, Digoxin and Oral contraceptives.

Adverse effects

Rosuvastatin calcium is generally well tolerated. The adverse events seen with rosuvastatin are generally mild and transient.

Central Nervous System:

Dizziness

Gastrointestinal:

Constipation, nausea, abdominal pain and pancreatitis (rare)

Musculoskeletal:

Myalgia, asthenia, myopathy (including myositis) and rhabdomyolysis (rare)

Skin:

Pruritus, rash, urticaria**,** hypersensitivity reactions including angioedema (rare)

Miscellaneous:

Headache

Indications and clinical uses

Rosuvastatin calcium is indicated as an adjunct to diet, at least equivalent to the Adult Treatment .Panel III (ATP III TLC diet), for the reduction of elevated total cholesterol, LDL-cholesterol, the total cholesterol: HDL-cholesterol ratio and triglycerides and for increasing HDL-C;in hyperlipidemic and dyslipidemic conditions, when response to diet and exercise alone has
been inadequate including:

- Primary hypercholesterolemia (Type IIa including heterozygous familial hypercholesterolemia and severe non-familial hypercholesterolemia)
- Combined (mixed) dyslipidemia (Type IIb)
- Homozygous familial hypercholesterolemia where rosuvastatin calcium is used either alone or as an adjunct to diet and other lipid lowering treatment such as aphaeresis.

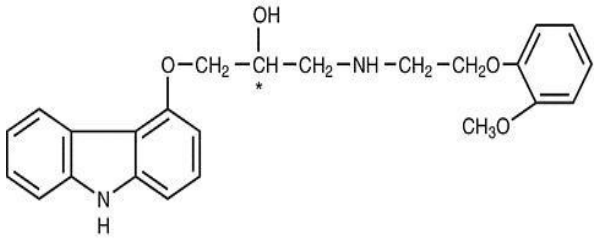
Contraindications

- Rosuvastatin calcium is contraindicated in patients with a known hypersensitivity to any component of this product.
- Rosuvastatin is contraindicated in patients with active liver disease orwith unexplained persistent elevations of serum transaminases.
- HMG-Co-A reductase inhibitors are contraindicated during pregnancy and in nursing mothers.

CARVEDILOL[61,62,63,64]:

Carvedilol is a nonselective β-adrenergic blocking agent with additional α1-blocking activity.

Chemical structure :



Chemical name	**:**	1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy) ethyl] amino]- 2-propanol
Molecular weight	**:**	406.47
Molecular formula	**:**	$C_{24}H_{26}N_2O_2$
Category	**:**	Non selective β –adrenergic blocker with α1 – blocking activity

Dosage & administration: 3.125, 6.25, 12.5 to 25 mg per day orally.

Description	**:**	A white or almost white crystalline powder; Colorless crystals from ethyl acetate .
Solubility	**:**	Freely soluble in DMSO; soluble in methylene chloride (CH2Cl2); Methanol; sparingly soluble in ethanol, isopropanol; slightly soluble in ethyl ether; practically insoluble in water & dilute acids .
Melting point	**:**	114 – 115^0C

Mechanism of action:

- Carvedilol is a racemic mixture in which nonselective β-adrenoreceptor blocking activity is present in the S(-) enantiomer and α_1-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency.
- Carvedilol has no intrinsic sympathomimetic activity.Carvedilol beta adrenergic receptor blocking ability decreases the heart rate, myocardial contractility and

myocardial oxygen demand. Carvedilol also decreases systemic vascular resistance via its alpha adrenergic receptor blocking properties.

Absorption:

Carvedilol is rapidly and extensively absorbed following oral administration, with an absolute bioavailability of approximately 25% to 35% due to a significant degree of first-pass metabolism. Plasma concentrations achieved are proportional to the oral dose administered. When administered with food, the rate of absorption is slowed, as evidenced by a delay in the time to reach peak plasma levels, with no significant difference in extent of bioavailability.

Half-life ($t_{1/2}$):

7 to 10 hrs

Volume of Distribution (V_d):

115 L

Protein binding:

98 %, primarily with albumin. The plasma-protein binding is independent of concentration over the therapeutic range.

Metabolism:

Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile into the feces. Demethylation and hydroxylation at the phenol ring produce 3 active metabolites with β-receptor blocking activity. the 4'-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol for β-blockade.

Elimination:

Less than 2% of the dose was excreted unchanged in the urine. The metabolites of carvedilol are excreted primarily via the bile into the feces.

Clearance: 500 to700 mL/min.

Therapeutic indication :

In the treatment of

Hypertension,

Congestive heart failure,

Angina pectoris.

Drug interactions:

Digoxin,Insulin or oral hypoglycemics,Inducers and inhibitors of hepatic metabolism.

Contraindications

Hypersensitivity to carvedilol or any component of the product,

Pregnancy and lactation,

Cardiogenic shock,

History of bronchospasm or asthma.

3. EXCIPIENT PROFILE

PHARMACEUTICAL EXCIPIENTS:

Excipients are substances other than the pharmacologically active drug or prodrugs, which are included in the manufacturing process or contained in the pharmaceutical finished product or dosage form.

Excipients play a wide variety of functional role in pharmaceuticals dosage forms including,

- Modifies the solubility and bioavailability of active pharmaceutical ingredients (APIs).
- Increasing the stability of active ingredients the dosage forms.
- Maintaining the pH and/or osmolarity of liquid formulations.
- Helping active ingredients maintained preferred polymorphic Forms or conformation.
- Modulating immunogenic responses of active ingredients (e.g.adjuvants).

HYDROXY PROPYL METHYL CELLULOSE[65]

1. **Non-proprietary Name:**

   BP: Hypromellose, JP: Hypromellose PhEur: Hypromellose

   USP: Hypromellose

2. **Synonyms:**

   Benecel MHPC, E464, hydroxyl propyl methyl cellulose, HPMC hypromellosum, methocel, methyl cellulose propylene glycol ether, methyl hydroxylpropyl cellulose, metolose , MHPC,Pharmacoat, Tylophor, Tylose.

3. Chemical Name: Cellulose hydroxyl propyl methyl ether.

4. Molecular weight: Molecular weight approximately 10000-1500000.

5. **Functional category**:

Bio adhesive material, coating agent, controlled release agent, emulsifying agent,film forming agent, suspending agent, sustained release agent and tablet binder etc.,

6. Description:

Hypromellose is an odourless and tasteless, white or creamy – white fibrous or granular powder.

7. Solubility :

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%) and ether.

8. **Applications:**

HPMC is widely used in oral, ophthalmic, nasal and topical pharmaceutical formulations. It is used as tablet binder in film-coating and as a matrix for extended release tablet formulations, concentrations between 2-5% used as binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of drugs from a matrix at levels of 10-80%w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25-5.0%.

XANTHAN GUM[65]

1. Non-proprietary names:

BP, USP-NF: Xanthan gum, PhEur: Xanthani gummi

2. **Synonyms:**

Corn sugar gum, E415, Keltrol,poly saccharide B-1459, Rhodigel, Vansan NF, Xantural.

3. Chemical name: Xanthan gum

4. Empirical formula and Molecular weight:

$(C_{35}H_{49}O_{29})_n$. Xanthan gum as a high molecular weight polysaccharide gum. Itcontains D-glucose and D-mannose as a dominant hexose units, along with D-glucuronic acid and is prepared as the sodium, potassium or calcium salt.

5. Structural formula:

Each xanthan gum repeat units contains five sugar residues: two glucose, two mannose and one glucuronic acid. The polymer backbone consist of four b-D-glucose units linked the 1 and 4 positions and is therefore identical in structure to cellulose

6. Functional category:

Stabilizing agent; viscosity increasing agent; suspending agent.

7. **Description:**

Xanthan gum occurs as a cream or white colored odourless, free flowing, fine powder.

8. **Applications:**

Xanthan gum is widely used in oral and topical formulation cosmetics and food as a stabilizing agent. It is also used as emulsifying agent and thickening agent, it is nontoxic,compatible with most other pharmaceutical ingredients and has good stability and viscosity properties over wide pH and temperature range, it is also used as a matrix former in sustained release tablets, it increases the retention time of the ophthalmic solutions in eye and as bioadhesive polymer.

GUAR GUM[65]

1. Nonproprietary Names

BP :Guar galactomannan

Ph.Eur :Guar galactomanan

USP –NF: Guar gum

2. Synonyms

Galactosol,Guar flour, Jaguar gum, Meyprogat, Meyprodor, Meyprofin

3. Chemical Name and CAS Number

Galactomannan polysaccharide & [9000-30-0]

4. Empirical Formula and Molecular Weight

$(C_6H_{12}O_6)_n$ and 220.000

5. Description

Guar gum occurs as an odourless or nearly odourless, white to yellowish-white powder with a bland taste.

6. Solubility

Practically insoluble in organic solvents, cold or hot water, Guar gum disperses and swells almost immediately to form a highly viscous, thixotropic sol. The optimum rate of hydration occurs at pH 7.5 – 9.0.

7. Functional Category

Suspending agent, tablet binder, tablet disintegrant, viscosity increasing agent

8. Applications in Pharmaceutical Formulation or Technology

Guar gum is used in cosmetics, food products, and pharmaceutical formulations. It has also been investigated in the preparation of sustained release matrix tablets in the place of cellulose derivatives such as methylcellulose. In pharmaceuticals, guar gum is used in solid-dosage forms as a binder and disintegrant; in oral and topical products as a suspending, thickening and stabilizing agent; and also

as a controlled-release carrier. Guar gum has also been examined for use in colonic drug delivery & oral controlled release formulations.

9. Stability and Storage Conditions

Aqueous guar gum dispersions have a buffering action and are stable at pH 4.0-10.5. However, prolonged action reduces the viscosity of dispersions. The bacteriological stability of guar gum dispersions may be improved by the addition of a mixture of 0.15%methylparaben and 0.02% propyl paraben as a preservative. In food applications, benzoic acid, citric acid, sodium benzoate or sorbic acid may be used. Guar gum powder should be stored in a well-closed container in a cool and dry place.

10. Incompatibilities

Guar gum is compatible with most other plant hydrocolloids such as tragacanth. Itis incompatible with acetone, ethanol (95%), tannins, strong acids and alkalis. Borate ions, if present in the dispersing water, will prevent the hydration of guar gum. However the addition of borate ions to hydrated guar gum produces cohesive structured gels and further hydration is then prevented. The gel formed can be liquefied by reducing the pH to below 7 or by heating. Guar gum may reduce the absorption of Penicillin V from some formulations by a quarter.

SODIUM STARCH GLYCOLATE[65]

1. Non-proprietary name

BP: Sodium starch glycolate, Ph.Eur: sodium starch glycolate.

2. Synonyms

Carboxymethyl starch, sodium salt, carboxy methyl amylum natricum; Explosol, glycolys, primojel, tablo, viva star p.

3. Chemical name:

Sodium carboxy methyl starch.

4. Functional category:

Tablet and capsule disintegrant.

5. Description:

Sodium starch glycolate is a white or almost white free- flowing hygroscopic powder.

6. Solubility:

Practically insoluble in methylene chloride; It gives a translucent suspension in water.

7. Applications:

It is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablet prepared by direct compression or wet granulation process. The usual concentration employed in formulation is between 2% and 8%, with the optimum concentration of about 4%.disintegration occurs by rapid uptake of water and enormous swelling. Increasing the tablet compression pressure also appears to have no effect on disintegration time.

CROSPOVIDONE[65]

1. Non-proprietary Name:

BP: Crospovidone PhEur: Crospovidonum USP-NF: Crospovidone

2. Synonyms:

Crosslinkedpovidone, E1202;Kollidon CL, Kollidon CL-M, Polyplasdone XL,Polyplasdone XL-10; polyvinylpolypyrrolidone,PVPP,1-vinyl-2-pyrrolidinone homopolymer.

3. Chemical Name:

1-Ethenyl-2-pyrrolidinone homopolymer.

4. Molecular weight: Molecular weight approximately >1 000 000

5. **Functional category**: Tablet disintegrant.

6. Description:

Crospovidone is a white to creamy-white, finely divided, freeflowing, practically tasteless, odourless or nearly odourless, hygroscopic powder.

7. Solubility:

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%) and ether.

8. **Applications:**

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

CROSCARMELLOSE SODIUM[65]

1. Non-proprietary Name:

BP: Croscarmellose sodium, PhEur: Croscarmellose natriumconexum USP: Croscarmellose sodium

2. Synonyms:

Ac-Di-Sol; cross linked carboxy methylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

3. Chemical Name: Cellulose, carboxy methyl ether, sodium salt.

4. Molecular weight: Molecular weight approximately 90000-700000

5. **Functional category**:Tablet and capsule disintegrant

6. Description:

Croscarmellose sodium occurs as an odourless, white or grayish white powder

7. Applications:

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extra granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet granulation process.

8. Incompatibilities

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

POVIDONE[65]

1. Nonproprietary name

Povidone

2. Synonyms:

E1201, kollidon, plasdone, poly[1-(2-oxo-1-pyrolidinyl) ethylene] polyvidone;polyvinyl pyrrolidone, povidone, PVP; povipharm 1-vinyl-2-pyrolidone polymer.

3. Chemical name: 1-ethenyl-2-pyrollidone homo polymer.

4. Empirical formula: $(C_6H_9NO)_n$

5. Molecular weight: 2500-3,000,000

6. Functional category:

Disintegrant, dissolution enhancer, suspending agent, tablet binder.

7. Description:

Povidone occurs as a fine, white to creamy-white colored, odourless or almost odourless, hygroscopic powder. Povidone with equal to or lower than 30 are manufactured by spray drying and occurs as spheres. Povidone K90 and higher k-values manufactured drum drying and occurs as plates.

8. Incompatibilities:

Incompatible with in organic salts, natural and synthetic resins.

9. Application:

In tablets, Povidone solutions are used as binders in wet granulation processes. Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol or hydro alcoholic solutions. It is used as a solubilizer in oral and parenteral formulations. Povidone is used as a coating agent. Povidone is additionally used as suspending; stabilizing and viscosity increasing agent in topical and oral suspensions and solutions. The solubility of poorly soluble drugs can be increased by mixing with povidone.

SODIUM BICARBONATE[65]

1. Non-proprietary name:

BP: Sodium bicarbonate, JP: Sodium bicarbonate, PhEur: Natrii hydrogeno carbonas, USP: Sodium bicarbonate

2. Synonyms:

Baking soda, E500, Effer –soda,monosodium carbonate, Sal de vichy, Sodium acid carbonate, sodium hydrogen carbonate.

3. Chemical Name:

Carbonic acid monosodium salt

4. Empirical Formula:

$NaHCO_3$ 84.01

5. Functional Category:

Alkalizing and therapeutic agents

6. **Description:**

Sodium bicarbonate occurs as an odourless, white, crystalline powder with saline, slightly alkaline taste. The crystal structure is monoclinic prisms.

7. Incompatibilities:

Reacts with acids, acidic salts and alkaloidal salts

8. Applications:

Sodium bicarbonate is used as a source of CO2 in the formulation or technology effervescent tablets and granules. In effervescent tablet and granules, sodium bicarbonate is usually formulated with citric acid or tartaric acid; tablets prepared with sodium bicarbonate alone since the gastric fluid is sufficient to produce the effervescences; it is also used in tablet formulations to buffer the drug molecules that are weak acids, thereby increasing the rate of dissolution and reducing gastric irritation. Recently it is used as a gas generating agent in floating systems and alginate raft systems.

LACTOSE[65]

1. Non-proprietary Names:

BP: Lactose, PhEur: Lactose Monohydrate, USP-NF: Lactose monohydrate

2. **Synonyms:**

CapsuLac, GranuLac, Lactochem; lactosum monohydricum Monohydrate; Pharmatose, PrismaLac, SacheLac, SorboLac, SpheroLac, SuperTab 30GR, Tablettose.

3. Chemical Name: O-b-D-Galactopyranosyl-(1-4)-a-D-glucopyranose monohydrate

4. **Empirical Formula:** $C_{12}H_{22}O_{11}$. H_2O

5. **Molecular Weight:** 360.31

6. **Functional Category:**

Dry powder inhaler carrier, lyophilisation aid, tablet binder, tablet and capsule diluents, tablet and capsule filler.

7. **Description:**

The stable crystalline forms of lactose are a-lactose monohydrate, b-lactose anhydrous, and stable α -lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder. Lactose is odourless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet.

8. **Solubility:**

Practically insoluble in chloroform, ethanol, ether; Soluble in water.

9. **Applications:**

Lactose is widely used as a filler and diluent in tablets and capsules. Lactose is also used as a diluent in dry-powder inhalation. Lactose is also used in the manufacture of dry powder formulations for use as aqueous film-coating solutions or suspensions. Lactose is also used in combination with sucrose (approximately 1: 3) to prepare sugar coating solution.

MAGNESIUM STEARATE[65]

1. Non-proprietary names:

BP:Magnesium stearate, JP: magnesium stearate, PhEur:magnesium stearate, USP-NF:Magnesium stearate.

2. Synonyms:

Dibasic magnesium stearate, Magnesiudi stearate; Magnesia stearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; Synpro 90.

3. Chemical name:

Octadecanoic acid, Magnesium salt.

4. Empirical formula:

$C_{36}H_{70}MgO_4$

5. Molecular weight:

591.24

6. Functional category:

Tablet and capsule lubricant.

7. Description:

Magnesium stearate is a very fine, light white, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

8. Incompatibilities:

Incompatible with strong acids, alkalis and iron salts.

9. Applications:

It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0%w/w. It is hydrophobic and may retard the dissolution of a drug from solid dosage form. The lowest possible concentration is therefore used in such formulations.

TARTRAZINE[65]

Empirical formula:

$C_{16}H_9N_4Na_3O_9S_2$

Molecular weight:

534.39

CAS number:

[1934-21-0]

Synonyms:

4,5-dihydro-5-oxo-1-(4-sulfophenyl)-4-[(4-sulfophenyl)azo]-1*H*-pyrazole-3-carboxylic acid tri sodium salt; E102; FD&C yellow #5; hydrazine yellow.

Appearance:

yellow or orange-yellow powder. Aqueous solutions are yellow-colored; the color is retained upon addition of hydrochloric acid solution, but with sodium hydroxide solution a reddish color is formed.

Absorption maximum:

425 nm

Color Index No.:

CI 19140

Use:

It is used to improve the appearance of a product and to impart a distinctive coloring for identification purposes.

Table.3: List of materials and their applications in formulation

S.No	Name of material	Manufacturer /Supplier	Use in formulation
1.	Rosuvastatin calcium	Madras Pharma Pvt.Ltd.	Active ingredient
2.	Carvedilol	Madras Pharma Pvt.Ltd.	Active ingredient
3.	HPMC K 100	Kniss Laborataries	Hydrophilic polymer
4.	Xanthan gum	Kniss Laborataries	Hydrophilic polymer
5.	Guar gum	Kniss Laborataries	Hydrophilic polymer
6.	Sodium starch glycolate	KnissLaborataries	Super disintegrant
7.	Crospovidone	KnissLaborataries	Super disintegrant
8.	Croscarmellose Sodium	KnissLaborataries	Super disintegrant
9.	PVP K30	KnissLaborataries	Binding agent
10.	Sodium bicarbonate	Indian Research products	Gas generating agent
12.	Magnesium stearate	Indian Research products	Lubricant
13.	Tartrazine	Kwality pharmaceuticals	Colorant

Table 4: List of equipments used

S.No	Equipment's / Instruments	Manufacturer / Supplier
1.	Electronic weighing balance	Asha scientific company, Mumbai
2.	10 Station compression machine	Rimek, India
3.	Vernier calliper	Mitutoyo, Japan
4.	Monsanto hardness tester	Erweka, Mumbai
5.	Friabilator	Electrolab, India
6.	pH meter	MC Dalal, Chennai
7.	Disintegration apparatus	Electrolab, India
8.	Dissolution testing apparatus	Veego, India
9.	UV-visible spectrophotometer	1800-Shimadzu, Japan
10.	Fourier Transform Infra-Red Spectrophotometer	Shimadzu, Japan

PREFORMULATION STUDIES

The Preformulation studies are conducted to establish the physiochemical characteristics of the drug and its compatibility with the excipients used. The Preformulation studies are necessary to formulate drug into stable, safe and effective dosage form.

Drug-excipient compatibility study

The drug and excipients selected for the formulation are evaluated for physical and chemical compatibility studies.

Physical compatibility study

The physical compatibility studies are conducted to provide valuable information to the formulator in selecting the appropriate excipients for the formulation. It was done by mixing the drugs and excipients and placed at room temperature, 40°C and 75%RH. Any color change of the physical mixture was observed visually.

Chemical compatibility study[66]

Pure drugs, polymers, excipients, drug-excipient mixture was subjected to FTIR to investigate the drug-excipient interactions. The IR spectra of test samples are obtained using potassium bromide pellet method**.**

Potassium bromide pellet method:

A small amount of finely ground solid sample is intimately mixed with about 100times its weight of powdered potassium bromide. The finely ground mixture is then passed under very high pressure in a press (at least 25,000 psig) to form a small pellet(about 1-2 mm thick and 1 cm in diameter). The resulting pellet is transparent to IR radiation and is run as such.

PREPARATION OF CALIBRATION CURVE:

Preparation of 0.1N HCl (pH 1.2)[60]:

8.5 ml of the hydrochloric acid was measured and dissolved 1000 ml of distilled water.

Calibration curve forRosuvastatinCalcium[21] :

100 mg of Rosuvastatin Calcium was weighed and transferred to a 100ml standard flask. The drug was dissolved in 10ml of methanol and made upto 100ml using 0.1N HCL in standard flask. From the above solution 10ml was taken and made upto 100ml using 0.1N HCL. From the above solution 2ml,4ml, 6ml,8ml,10ml are taken and made upto 100ml using 0.1N HCL. The absorbances of resulting solutions are measured at 252 nm using UV spectrophotometer. Calibration curve was plotted.

Calibration curve forCarvedilol[26] :

100 mg of Carvedilol was weighed and transferred to a 100ml standard flask. The drug was dissolved in 10 ml of methanol and made up to 100ml using 0.1N HCL in standard flask. From the above solution 10ml was taken and made up to 100ml using 0.1N HCL. From the above solution 2ml,4ml, 6ml,8ml,10ml are taken and made up to 100ml using 0.1N HCL. The absorbances of resulting solutions are measured at 241 nm using UV spectrophotometer. Calibration curve was plotted.

PRECOMPRESSION STUDIES OF DRUGS AND BLENDS:

FLOW PROPERTY MEASUREMENTS

The flow properties of powers are critical for an efficient tableting operation. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. The flow property measurements include bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio. The flow property measurements of drugs and blends are determined to select the type of granulation to be carried out in the formulation.

a) BULK DENSITY (ρ_b)[64]

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$\rho_b = M / V_b$$

Where,

M and V_b are mass of powder and bulk volume of the powder respectively.

b) TAPPED DENSITY(ρ_t)[64]

It is the ratio of weight of the powder to the tapped volume of powder. The powder was introduced into a measuring cylinder with the aid of funnel and tapped for300 times on a wooden surface at a 2 sec interval and the volume attained is the tappedvolume. It is expressed in g/ml and is given by

$$\rho_t = M / V_t$$

Where,

M and $V_t$are mass and tapped volume of the powder respectively.

c) CARR'S INDEX (OR) % COMPRESSIBILITY[64]

It indicates powder flow properties. It is measured for determining the relative importance of inter particulate interactions. It is expressed in percentage and is given by

$$CI = \frac{\rho_t - \rho_b \times 100}{\rho_t}$$

Where, ρ_t and ρ_b are tapped density and bulk density respectively.

d) HAUSNER RATIO[64]

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\mathbf{HR = \rho_t / \rho_b}$$

Where,

$\mathbf{\rho_t}$ and $\mathbf{\rho_b}$ are tapped density and bulk density respectively.

e) ANGLE OF REPOSE (θ)[64]

The flow properties were characterized in terms of angle of repose, Carr's index and Hausner's ratio. For determination of angle of repose (θ), the drug and the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The drug or the blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation.

$$\mathbf{\theta = \tan^{-1}(h/r)}$$

Where,

h = height of pile in cm; **r** = radius of pile in cm

Table 5: Values of Angle of Repose, Compressibility Index and Hausner's Ratio[64]

Flow Property	Angle ofRepose (in degrees)	Compressibility Index (%)	Hausner's Ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very Poor	>65	>38	>1.60

FORMULATION DEVELOPMENT

Formulation of Immediate release tablets of Rosuvastatin Calcium[44]

The immediate release tablets of Rosuvastatin Calcium (R1, R2 and R3) wereprepared by direct compression technique, using various super disintegrants such as Sodium Starch Glycolate (SSG), Croscarmellose Sodium (CCS) and Crospovidone. The tablets were prepared by using 10 station tablet compression machine.

Table.6:Formulation table for immediate release tablet of Rosuvastatin Calcium

S.No.	INGREDIENTS	R1	R2	R3
1.	Rosuvastatin Calcium	10	10	10
2.	Sodium starch glycolate	4	-	-
3.	Crospovidone	-	5	-
4.	Croscarmellose sodium	-	-	2
5.	PVP K30	3	3	3
6.	Lactose	80	79	82
7.	Magnesium stearate	3	3	3

Total weight of the tablet = 100 mg

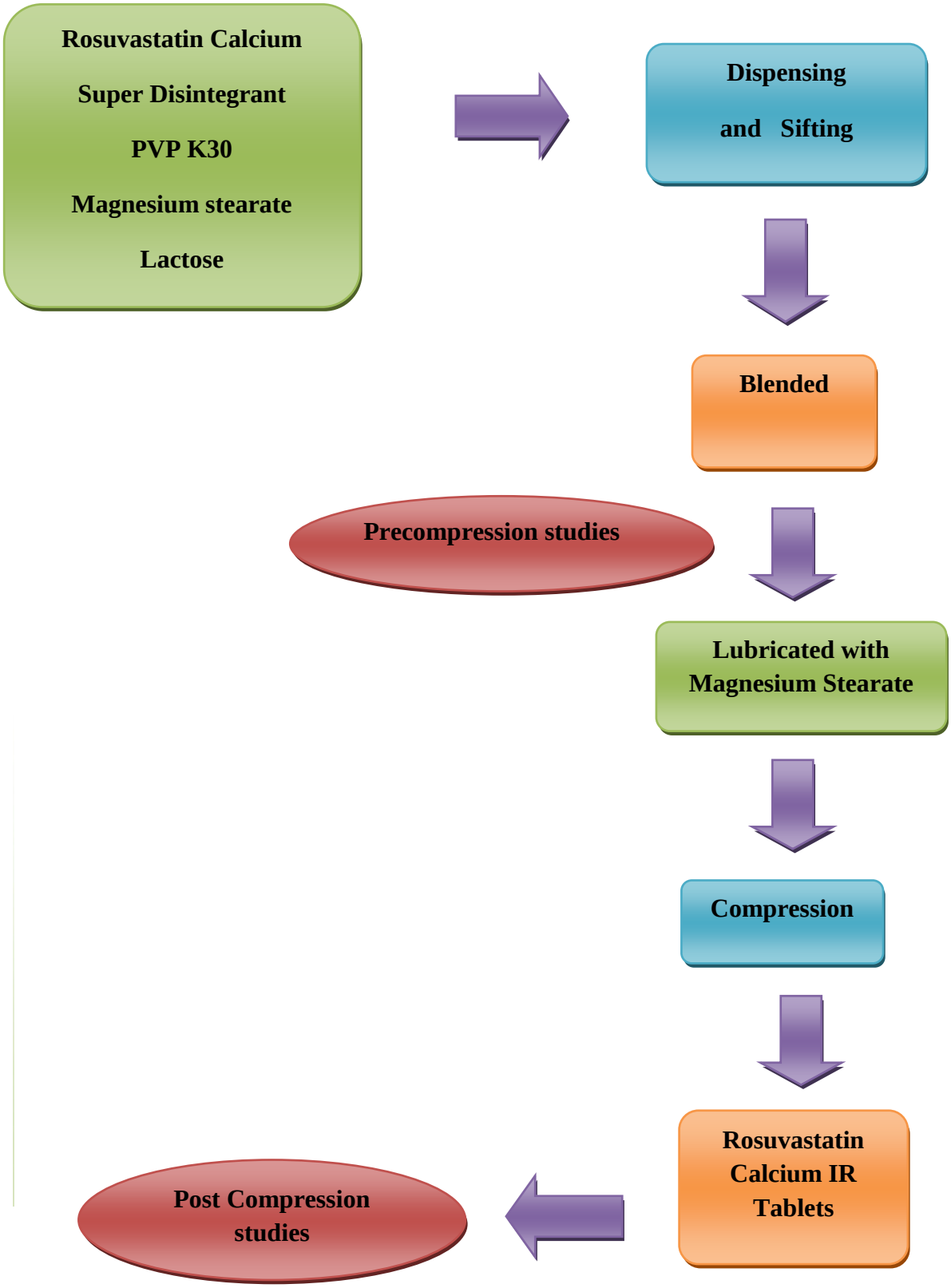


Fig.11: Flowchart for formulation of immediate release Rosuvastatin calcium tablets

Formulation of Carvedilol floating tablets[26]

The controlled release tablets of Carvedilol were prepared by direct compression technique. Different polymers such as Xanthan gum, Guar gum and HPMC K 100 are used.The concentrations of Xanthan gum and Guar gum were taken as variables. The powder blend was compressed by 10 station tablet compression machine using 8mm punches. The optimized batch of floating tablets of Carvedilol was then compressed with the optimized batch of immediate release Rosuvastatin Calcium tablets to get bilayer tablets.

Table 7: Formulation table for Carvedilol floating tablets

S.No.	Ingredients	C1	C2	C3	C4	C5	C6	C7	C8
1.	Carvedilol	25	25	25	25	25	25	25	25
2.	Xanthan gum	-	-	-	-	50	60	70	80
3.	Guar gum	50	60	70	80	-	-	-	-
4.	HPMC K 100	100	100	100	100	100	100	100	100
5.	Sodium Bicarbonate	50	50	50	50	50	50	50	50
6.	PVP K30	12	12	12	12	12	12	12	12
7.	Lactose	54	44	34	24	54	44	34	24
8.	Magnesium stearate	9	9	9	9	9	9	9	9

Total weight of the tablet = 300 mg

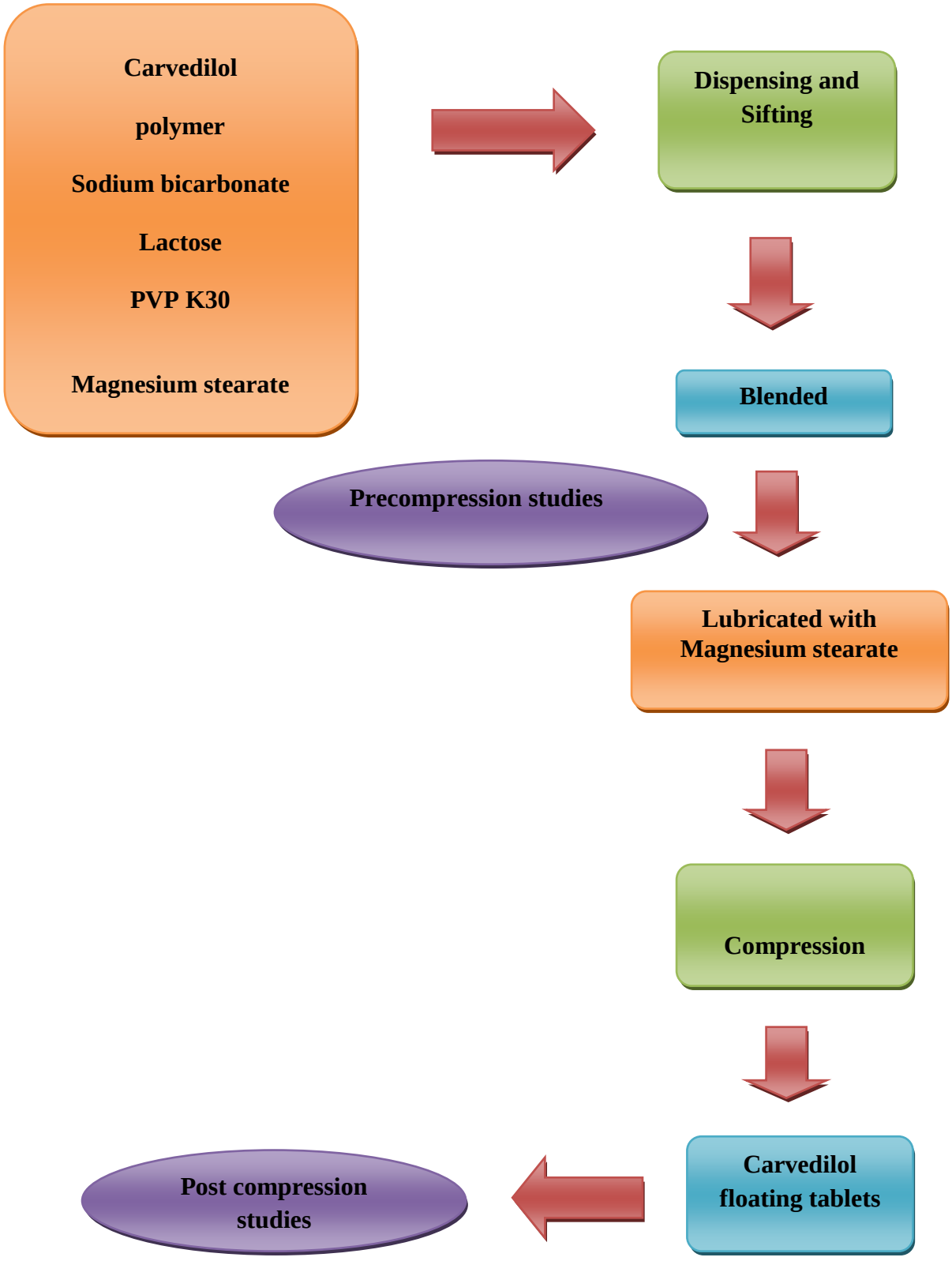
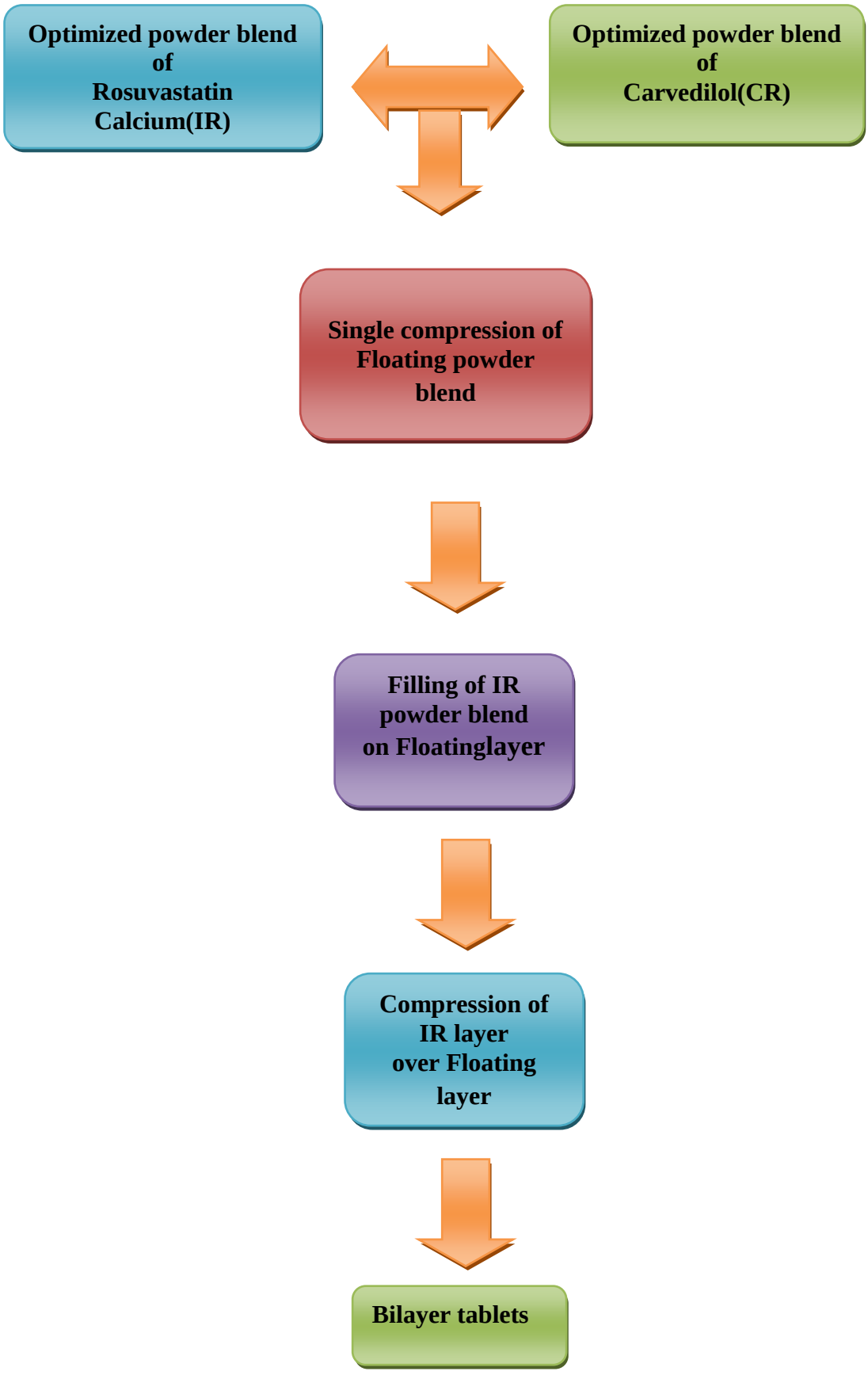


Fig.12 : Flowchart for formulation of Carvedilol floating tablets

Fig.13: Flowchart for formulation of bilayer tablets



POST COMPRESSION STUDIES

PHYSICAL PARAMETERS

1. General appearance:

The general appearance of the tablets from each formulation batch was observed.The general appearance parameters are shape, color, presence or absence of odor and taste were evaluated visually.

2. Uniformity of weight:

Twenty tablets were selected at a random and weighed individually. The averageweight was also measured. The percentage deviation of tablets was calculated andcompared with standard specifications.

Table 8: Uniformity of weight

S.No	Average weight of tablet	% Deviation
1.	80 mg or less	10
2.	80 to 250 mg	7.5
3.	More than 250 mg	5

3. Thickness and diameter:

The thickness and diameter was measured to determine the uniformity of size and shape. Thickness and diameter of the tablets were measured using Vernier caliper.

4. Hardness:

Hardness is defined as the force required for breaking a tablet at diametric compression test and it is termed as tablet crushing strength. Hardness of the prepared formulations was determined using Monsanto hardness tester. It was expressed in kg/cm2

5. Friability:

Friability of the prepared formulations was determined by using Rochelle Friabilator. Pre-weighed sample of tablets was placed in the friability tester, which was then operated for 100 revolutions. Tablets were dedusted and reweighed. The friability of the tablets was calculated using the formula mentioned below,

$$\text{Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablet}}{\text{Initial weight of the tablets}}$$

6. Disintegration:

Randomly six tablets were selected from each batch for disintegration test. Disintegration test was performed without disc in simulated gastric fluid (37+ 0.50C) using United States Pharmacopeia (USP) disintegration apparatus. The mean standard deviations (SD) of six tablets were calculated.

DRUG CONTENT

I) FOR IR TABLETS CONTAINING ROSUVASTATIN CALCIUM

Twenty tablets were selected randomly, weighed and finely grinded. An accurately weighed quantity of powder equivalent to 10 mg of Rosuvastatin Calcium was transferred to a 100 volumetric flask and dissolved in 10 ml of methanol and the volume was made up to the mark with 0.1N HCl. The solution was filtered and 10 ml of the filtrate was further diluted with 0.1N HCl in a 100ml volumetric flask. From above solution 10ml was taken and diluted with 0.1N HCL in 100 ml flask. The absorbance of the resulting solution was measured at 252 nm taking 0.1N HCl as blank using UV Visible Spectrophotometer. The concentration was obtained from the calibration graph.

II) FOR FLOATING TABLETS CONTAINING CARVEDILOL

Twenty tablets were selected randomly, weighed and finely grinded. An accurately weighed quantity of powder equivalent to 25 mg of Carvedilol was transferred to a 100 volumetric flask and dissolved in 10 ml of methanol and the volume was made upto the mark with 0.1N HCl. The solution was filtered and 10 ml of the filtrate was further diluted with 0.1N HCl in a 100ml volumetric flask. From above solution 10ml was taken and diluted with 0.1N HCL in 100ml flask. The absorbance of the resulting solution was measured at 241 nm taking 0.1N HCl as blank using UV Visible Spectrophotometer. The concentration was obtained from the calibration graph.

III) BILAYER FLOATING TABLETS CONTAINING SIMVASTATIN AND TELMISARTAN BY SIMULTANEOUS ESTIMATION METHOD[47]

Simultaneous estimation of Rosuvastatin calcium and Carvedilol was carried out using UV spectrophotometer.

PROCEDURE:

The following equations were used to determine the contents.

$$Cx = \frac{A_2ay_1 - A_1ay_2}{ax_2\,ay_1 - ax_1\,ay_2}$$

$$Cy = \frac{A_1ax_2 - A_2ax_1}{ax_2\,ay_1 - ax_1\,ay_2}$$

Where,

ax_1 and ax_2= the absorptivity of drug X at λ_1 and λ_2 respectively

ay_1 and ay_2= the absorptivity of drug Y at λ_1 and λ_2 respectively

A_1 and A_2 = the absorbance of sample at λ_1 and λ_2 respectively

In 1990, Glen suggested a criterion for obtaining maximum precision, based on absorbance ratios[68]

$$\frac{A_2/A_1}{ax_2/ax_1} \quad \text{and} \quad \frac{ay_2/ay_1}{A_2/A_1}$$

The ratios should lie outside the range of 0.1-2.0 for the precise determination of X and Y drugs respectively. This criterion is satisfied only when the λ max of the two components is reasonably dissimilar and the two components should not interact chemically.

Preparation of standard stock solution of Rosuvastatin Calcium:

100 mg of Rosuvastatin calcium was accurately weighed; 10 ml of methanol was added and further diluted to 100ml with 0.1N HCl. From above solution 10ml was taken and diluted to 100ml with 0.1N HCl. The absorbance of the solution was recorded at 252 nm and 241 nm.

Preparation of standard stock solution of Carvedilol:

100 mg of Carvedilol was accurately weighed; 10 ml of methanol was added and further diluted to 100ml with 0.1N HCl. From above solution 10ml was taken and diluted to 100ml with 0.1N HCl. The absorbance of the solution was recorded at 252 nm and 241 nm.

Preparation of sample solution:

Twenty tablets were selected randomly and the average weight was calculated. The tablets were then ground to a fine powder. The powder equivalent to the average weight of tablets was dissolved in 20 ml of methanol. The solution was made up to 100 ml with 0.1N HCL. 10 ml of the solution was diluted to 100 ml using 0.1N HCL in a separate standard flask. The absorbance of the solution was recorded at 252 nm and 241 nm. The amount of Rosuvastatin Calcium and Carvedilol were determined by simultaneous estimation method.

***IN-VITRO* DISSOLUTION STUDIES:**

For IR tablets:

The release of Rosuvastatin calcium was determined using USP Type II (Paddle) dissolution apparatus under sink condition. The dissolution medium was 900 ml of a0.1N HCl solution (pH=1.2), at 370c±0.20c and the stirring speed of 50 rpm. The *in-vitro* release studies were carried out for 1 hour. The absorbance of the solution was recorded at 291 nm using UV spectrophotometer.

For bilayer floating tablets:

The release of Rosuvastatin calcium and Carvedilol was determined using USP Type II(Paddle) dissolution apparatus under sink condition. The dissolution medium was 900 ml of a 0.1N HCl solution (pH=1.2), at 370c±0.20c and the stirring speed of 100 rpm. Aliquot(10ml) of the solution was collected from the dissolution medium at 5,10,15, 20, 30,45 min and at1,2,3,4,5,6,7,8,9,10,11,12 and 24 hours and were replaced with fresh dissolution medium.The absorbance of the solution was recorded at 252nm and 241 nm using UV spectrophotometer.

SWELLING STUDIES OF FLOATING TABLETS[20]:

The extent of swelling was measured in terms of percentage weight gain by tablets. The swelling behaviour of all the floating tablets was studied. Swelling index was determined in 900 ml of 0.1N HCl solution(pH=1.2), at $37^0c \pm 0.5^0c$. At the end of 1,2,3,4,5,6,7,8,910,11,12 and 24 hours. Tablets were withdrawn and the excess of fluid was removed with a tissue paper. The tablets were weighed. The percentage weight gain by the tablet was calculated using the formula.

$$SI = \frac{M_t - M_0}{M_0} \times 100$$

Where,

SI= Swelling index

M_t= Weight of tablet at time t and

M_0= Weight of tablet at time 0

EVALUATION OF *IN-VITRO* RELEASE KINETICS[76]:

To study the *in-vitro* release kinetics of the optimized BFT, data obtained from dissolution study were plotted in various kinetics models.

1. Zero order equation :

The zero order release can be obtained by plotting cumulative % percentage drug released vs. time in hours. It is ideal for the formulation to have release profile of zero order to achieve pharmacological prolonged action.

$$C = K_0 t$$

Where,

K_0= Zero order constant

t= Time in hours

2. First order equation:

The graph was plotted as log % cumulative drug remaining Vs time in hours.

$$\text{Log } C = \log C_0 - Kt/2.303$$

Where,

C_0= Initial concentration of drug

K= First order

t= Time in hours

3. Higuchi kinetics:

The graph was plotted with % cumulative drug released vs. square root of time

$$\mathbf{Q = Kt^{½}}$$

Where,

K= constant reflecting design variable system (differential rate constant)

t= Time in hours

The drug release rate is inversely proportional to the square root of time

4. Hixon and Crowell erosion equation:

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixon and Crowell rate equation. The graph was plotted by cube root of % drug remaining vs. time in hours.

$$\mathbf{Q_0^{1/3} - Qt^{1/3} = K_{HC}Xt}$$

Where,

Qt= amount of drug released in time t.

Q_0= Initial Amount of drug

KHC= Rate constant for Hixon Crowell equation

5. Korsmeyer-Peppas equation:

To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug released Vs log time.

$$\mathbf{M_t/M_\alpha = Kt^n}$$

Where

$\mathbf{M_t/M_\alpha}$ **=** Fraction of drug released at time t

t = Release time

K= Kinetics constant (Incorporating structural and geometric characteristics of the formulation)

N= Diffusional exponent indicative of the mechanism of drug release.

Table9: Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non- Fickian) diffusion
0.89	Case II transport
n > 0.89	Super case II transport

PREFORMULATION STUDIES:
DRUG-EXCIPIENT COMPATIBILITY STUDY:

The drug-excipient compatibility study was conducted to reveal the excipient compatibility with the drug. The physical compatibility of drug and excipients were given in table 10.

Table 10: Physical compatibility study of Drug and Excipients

S. No.	Description and Conditions				
	Drug & Excipient	Initial	Room temperature and 400C/ 75% RH in days		
			10	20	30
1	ROS	Creamish white crystalline powder	NC	NC	NC
2	CAR	White crystalline powder	NC	NC	NC
3	Xanthan gum	Creamy white Free flowing fine powder	NC	NC	NC
4	Guar gum	White or creamy white Free flowing fine powder	NC	NC	NC
5	HPMC K 100	White or creamy white crystalline powder	NC	NC	NC
6	PVPK30	White or Creamy white colored Hygroscopic powder	NC	NC	NC
7	Sodium bicarbonate	White, crystalline powder	NC	NC	NC
8	Magnesium Stearate	White or off white crystalline powder	NC	NC	NC
9	Tartrazine	Yellowish orange coloured powder	NC	NC	NC
10	CAR + Xanthan gum	White, creamy white crystalline powder	NC	NC	NC
11	CAR+ Guar gum	White, creamy white crystalline powder	NC	NC	NC
12	CAR+ HPMC K 100	White, creamy white crystalline powder	NC	NC	NC
13	CAR+ PVPK30	White, almost white crystalline powder	NC	NC	NC
14	CAR+ Sodium Bicarbonate	White, almost white crystalline powder	NC	NC	NC
15	CAR+ Magnesium Stearate	White, almost white crystalline powder	NC	NC	NC
16	ROS+ CCS	White, creamy white crystalline powder	NC	NC	NC
17	ROS+CP	White, creamy white crystalline powder	NC	NC	NC

NC- No Change

The physical compatibility study was performed visually. The study implies that the drug and excipients were physically compatible with each other as there was no change in physical description.

CHEMICAL COMPATIBILITY STUDY

The possible interaction between the drug and the excipients used in the formulation was studied by FTIR spectroscopy. The results are given in the below

FTIR SPECTROSCOPY OF DRUGS

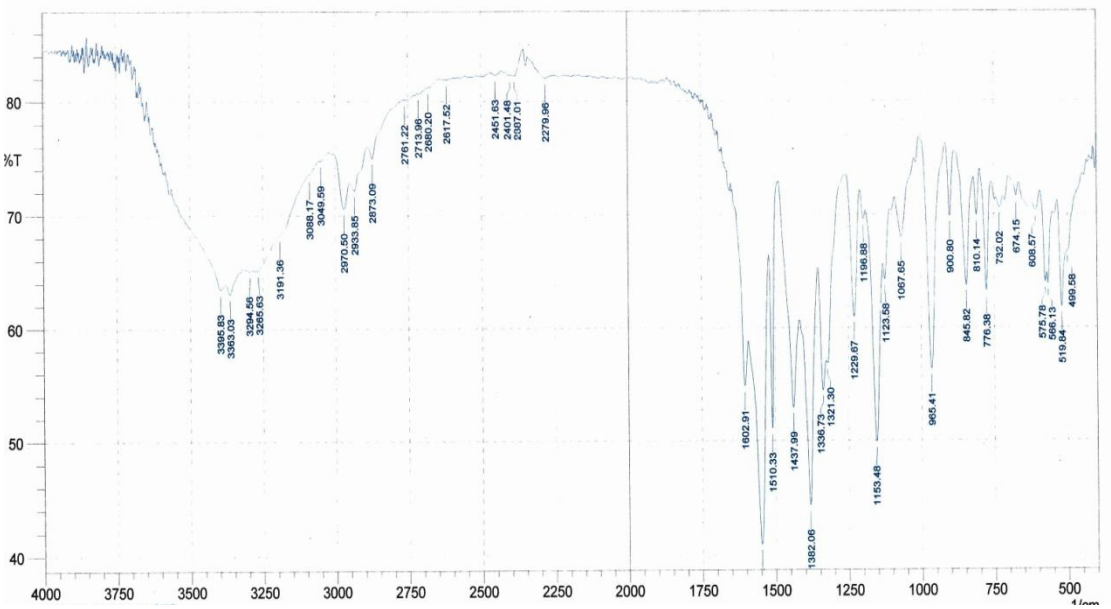


Fig 15: FTIR of Rosuvastatin Calcium.

Table 11: IR Spectral interpretation of Rosuvastatin Calcium

Wave number (cm^{-1})	Interpretation
3395	N-H Stretching
3200 -3550	O- H Stretching
3080	C-H Aromatic Phenol
2970	Alkane C-H Stretching
2873	Aldehyde C-H Stretching

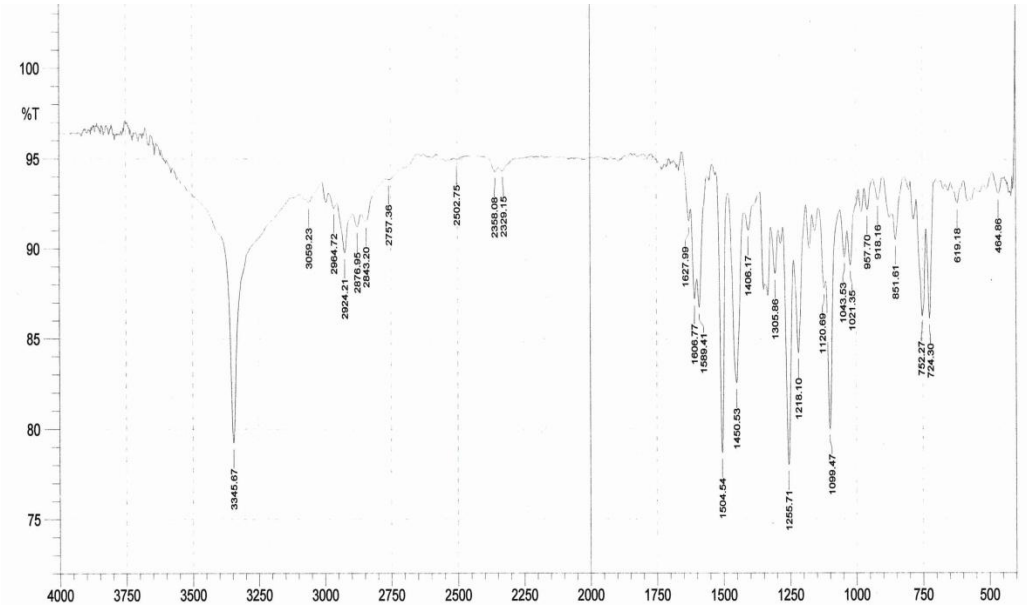


Fig 16: FTIR of Carvedilol.

Table 12: IR Spectral interpretation of Carvedilol.

Wave number (cm^{-1})	**Interpretation**
3345	N-H Stretching
2502	Carboxylic acid O-H Stretching
3059	Aromatic C-H
2964	Alkane C-H Stretching
2876	Aldehyde C-H Stretching

FTIR SPECTROSCOPY OF ROSUVASTATIN CALCIUM AND EXCIPIENTS

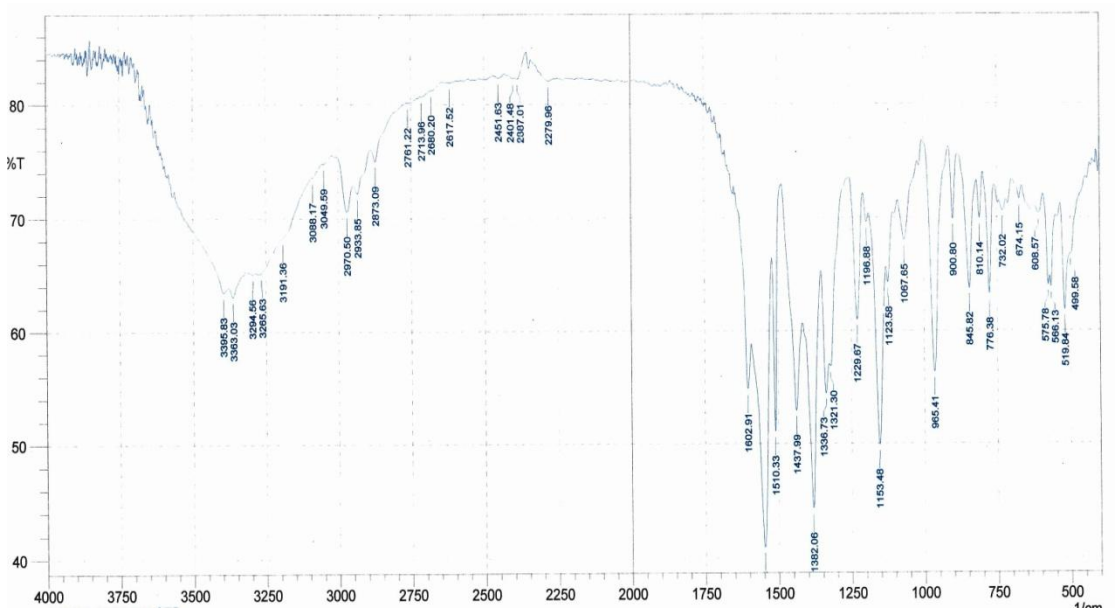


Fig 17: FTIR Spectroscopy of Rosuvastatin CalciumSodium Starch Glycolate (SSG)

Table 13: IR Spectral interpretation of Rosuvastatin Calcium with Starch Glycolate

Wave number (cm^{-1})	Interpretation
3345	N-H Stretching
2502	Carboxylic acid O-H Stretching
3059	Aromatic C-H
2964	Alkane C-H Stretching
2876	Aldehyde C-H Stretching

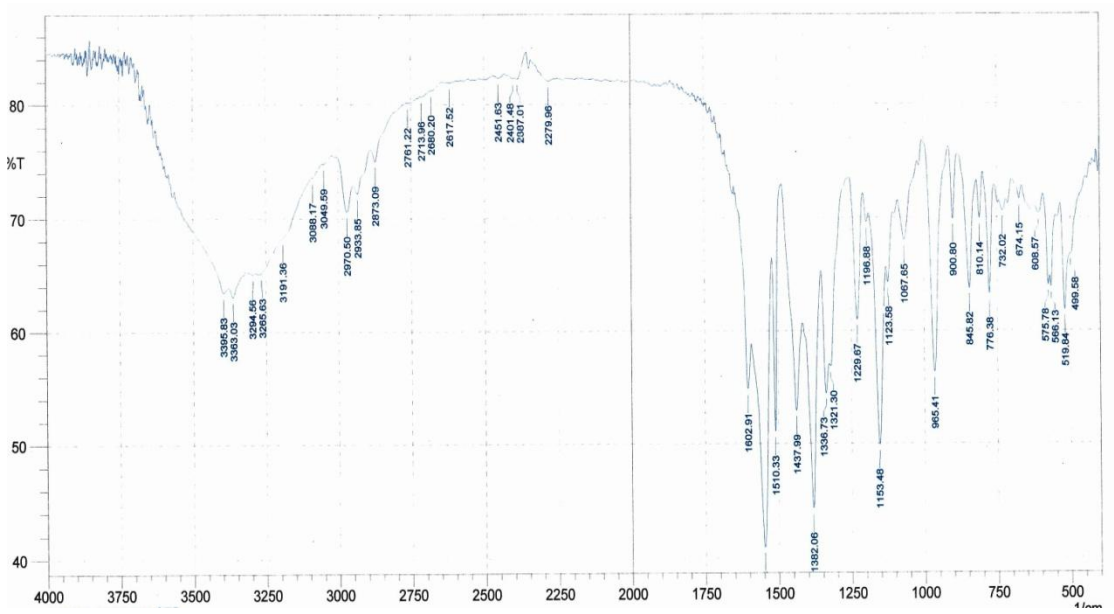


Fig 18: FTIR Spectroscopy of Rosuvastatin Calcium with Crospovidone

Table 14: IR Spectral Interpretation of Rosuvastatin Calcium with Crospovidone

Wave number (cm^{-1})	Interpretation
3345	N-H Stretching
2502	Carboxylic acid O-H Stretching
3059	Aromatic C-H
2964	Alkane C-H Stretching
2876	Aldehyde C-H Stretching

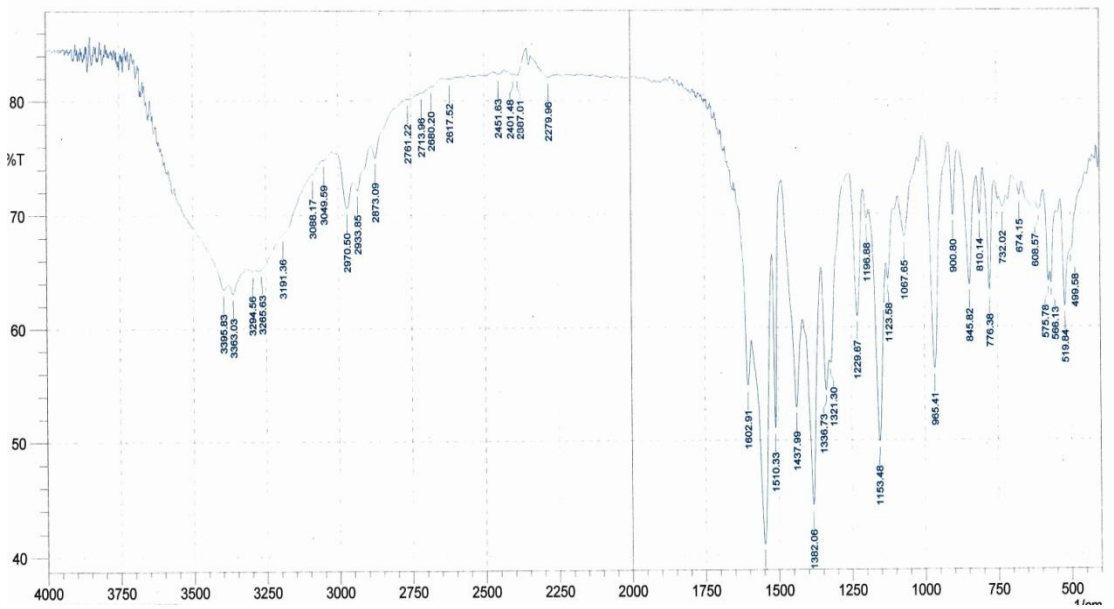


Fig 19: FTIR Spectroscopy of Rosuvastatin Calcium with Croscarmellose Sodium (CCS)

Table 15: IR Spectral interpretation of Rosuvastatin Calcium with Croscarmellose sodium

Wave number (cm^{-1})	Interpretation
3345	N-H Stretching
2502	Carboxylic acid O-H Stretching
3059	Aromatic C-H
2964	Alkane C-H Stretching
2876	Aldehyde C-H Stretching

FTIR SPECTROSCOPY OF CARVEDILOLAND EXCIPIENTS

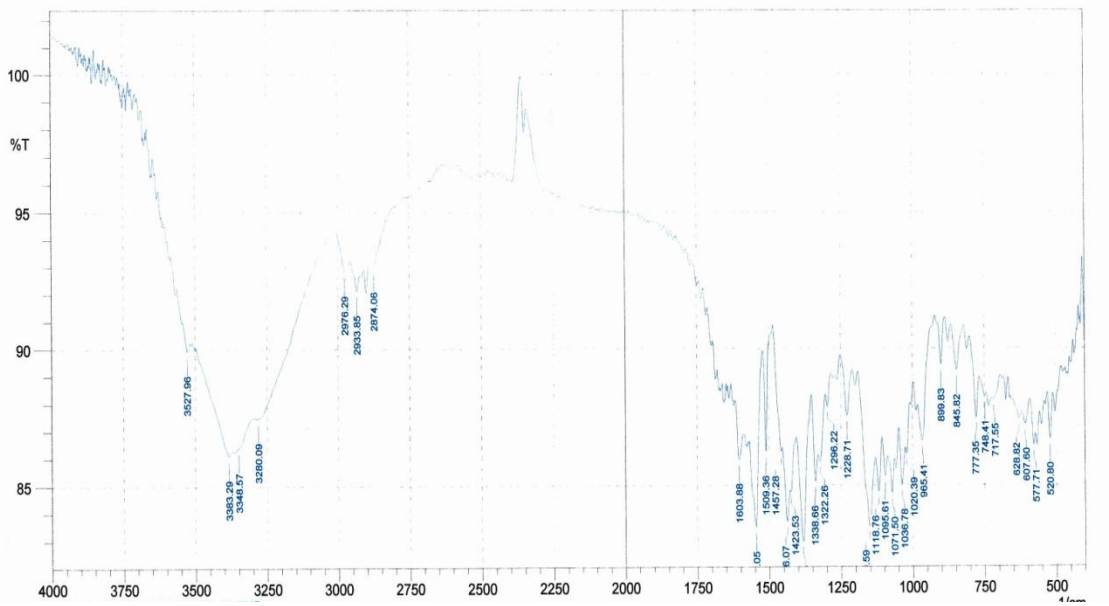


Fig 20: FTIR of Carvedilol with Xanthan gum

Table 16: IR Spectral interpretation of Carvedilol with Xanthan gum

Wave number (cm^{-1})	Interpretation
3345	N-H Stretching
2502	Carboxylic acid O-H Stretching
3059	Aromatic C-H
2964	Alkane C-H Stretching
2876	Aldehyde C-H Stretching

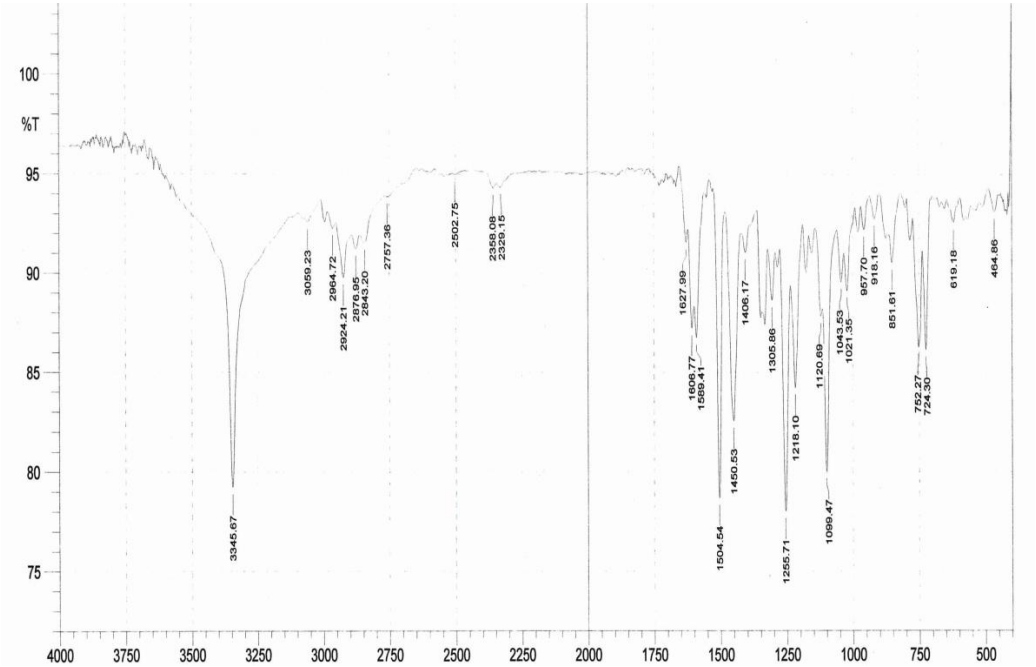


Fig 21: FTIR of Carvedilol with Guar Gum

Table 17: IR Spectral interpretation of Carvedilol with Guar Gum

Wave number (cm^{-1})	Interpretation
3345	N-H Stretching
2502	Carboxylic acid O-H Stretching
3059	Aromatic C-H
2964	Alkane C-H Stretching
2876	Aldehyde C-H Stretching

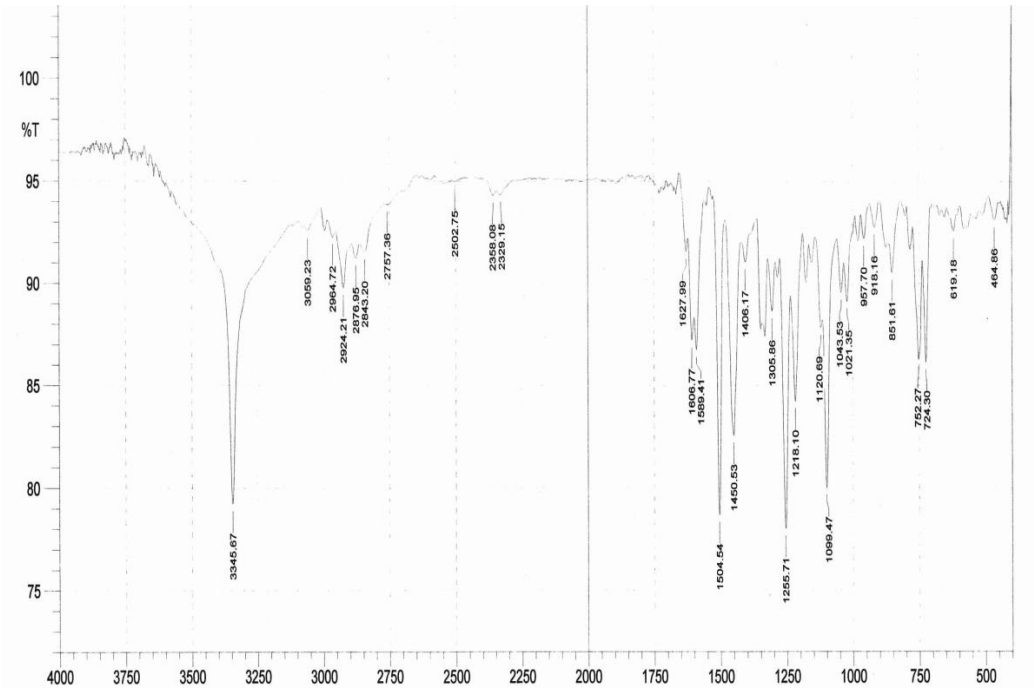


Fig 22: FTIR of Carvedilol with HPMC K 100

Table 18: IR Spectral Interpretation of Carvedilol with HPMC K 100

Wave number (cm^{-1})	Interpretation
3345	N-H Stretching
2502	Carboxylic acid O-H Stretching
3059	Aromatic C-H
2964	Alkane C-H Stretching
2876	Aldehyde C-H Stretching

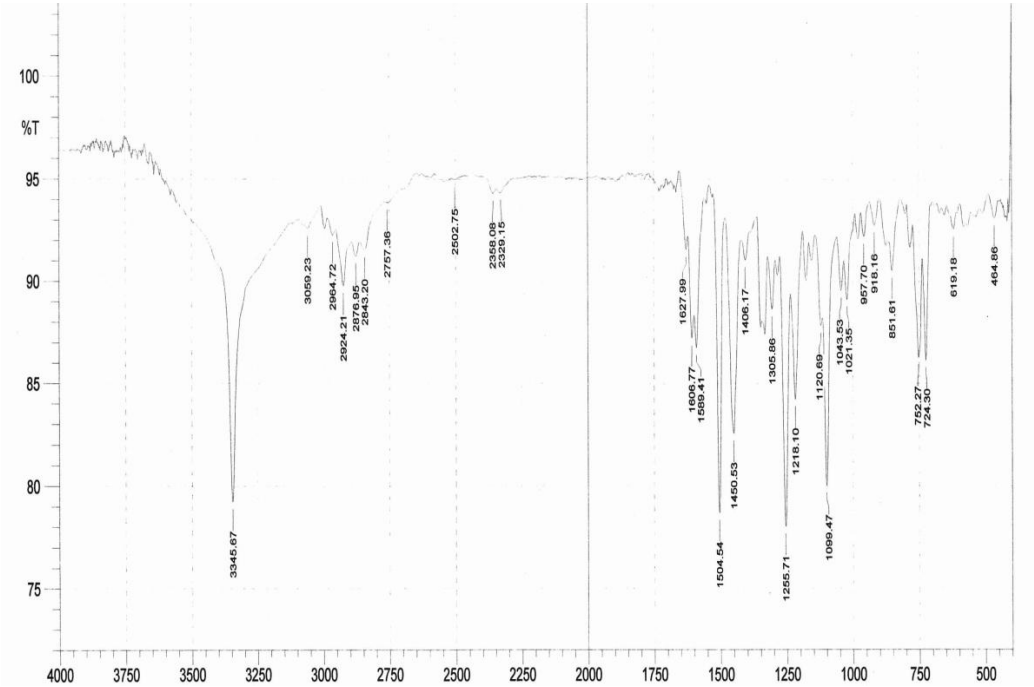


Fig 23: FTIR of Rosuvastatin Calcium powder blend

Table 19: IR Spectral Interpretation of Rosuvastatin calcium powder blend.

Wave number (cm^{-1})	Interpretation
3345	N-H Stretching
2502	Carboxylic acid O-H Stretching
3059	Aromatic C-H
2964	Alkane C-H Stretching
2876	Aldehyde C-H Stretching

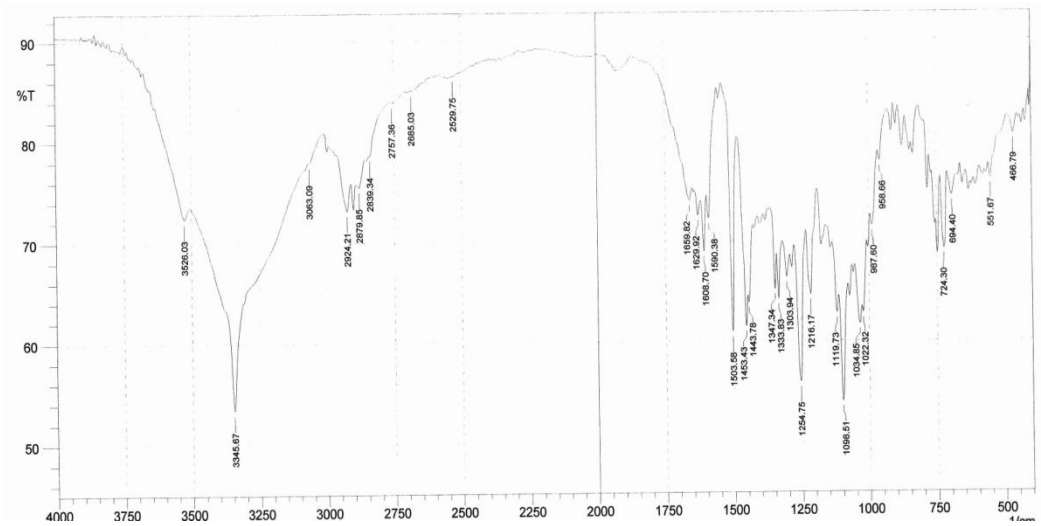


Fig 24: FTIR of Carvedilol powder blend

Table 19: IR Spectral Interpretation of Carvedilol powder blend

Wave number (cm^{-1})	Interpretation
3345	N-H Stretching
2502	Carboxylic acid O-H Stretching
3059	Aromatic C-H
2964	Alkane C-H Stretching
2876	Aldehyde C-H Stretching

The spectra indicated that there was no drug – excipient interaction as the peaks of the drug and the other excipients were seen in the drug excipient mixture. The study impliesthat the active ingredients and the excipients are chemically compatible with each other as there was no change in the IR spectral peaks.

CALIBRATION CURVE FOR ROSUVASTATIN CALCIUM

Table. 20: Data of calibration curve Rosuvastatin Calcium in 0.1N HCl

Concentration (µg/mL)	Absorbance at λ_{252nm}
0	0
2	0.064±0.0019
4	0.128±0.0053
6	0.190±0.0024
8	0.249±0.0094
10	0.319±0.0054

Mean n=3 R^2=0.9998

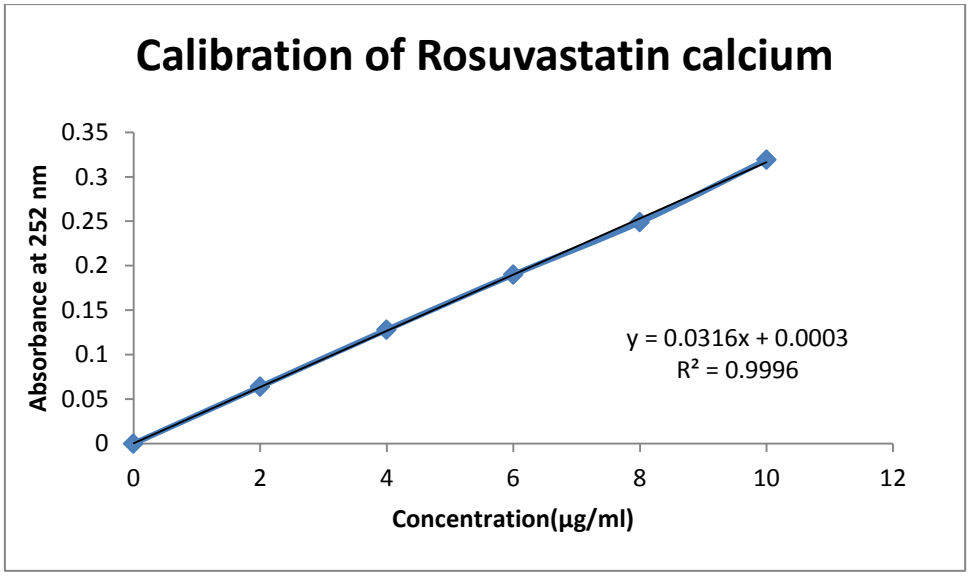


Fig.25:Calibration curve of Rosuvastatin Calcium

It was found that the solutions of Rosuvastatin calcium in 0.1 N HCl shows linearity (R^2=0.9998) in absorbance at concentrations of 2-10 µg/ml and obey beer Lambert's Law.

CALIBRATION CURVE FOR CARVEDILOL

Table.21:Data of calibration curve of Carvedilolin 0.1 N HCl.

Concentration (µg/ml)	Absorbance at λ_{241nm}
0	0
2	0.218 ±0.0097
4	0.469 ±0.0063
6	0.691 ±0.0032
8	0.940 ±0.0038
10	1.179 ±0.0233

R^2=0.9998

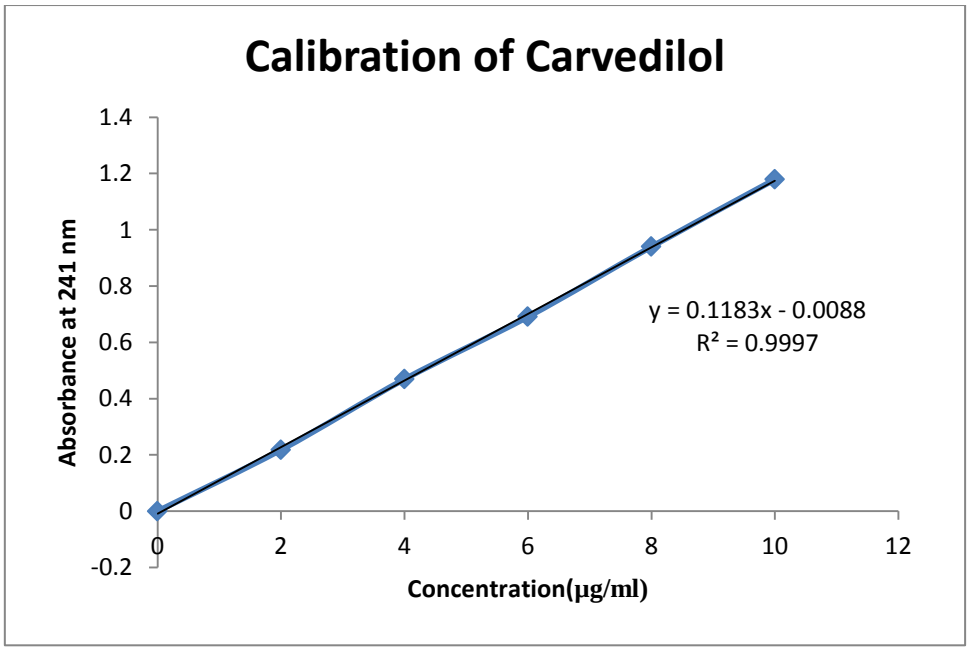


Fig.26: Calibration curve of Carvedilol

It was found that the solutions of Carvedilol in 0.1 N HCl show linearity(R^2=0.9998) in absorbance at concentrations of 2-10 µg/ml and obey Beer Lambert's Law.

FOR IR FORMULATION:

PRECOMPRESSION STUDIES:

The drug and the powder blends are evaluated for Precompression parameters. The results are given in the table.

Table.22:Precompression studies of drug and the powder blends without glidant

Drug Formulation	Bulk density* g/cm^3	Tapped density* g/cm^3	Compressibility index*(%)	Hausner's ratio*	Angle of repose* (degree)
Rosuvastatin Calcium	0.652±0.019	0.750± 0.025	13.08±0.438	1.15±0.0056	9.54±1.360
R1	0.511±0.026	0.594±0.016	13.99±1.995	1.163±0.026	35.22±0.02
R2	0.501±0.011	0.612±0.017	18.10±0.419	1.22±0.0061	33.53±1.09
R3	0.570±0.010	0.646±0.012	11.76±0.010	1.13±0.0053	27.54±0.02

The bulk density of the drug and IR Blends without lubricant ranged from 0.501 to 0.652 $g/cm^3$and tapped density ranged from 0.594 to 0.750 g/cm^3. The compressibility index of the drug and IR blend ranged from 11.76 to 18.10 % and Hausner's ratio ranged from 1.13 to 1.22. The angle of repose of IR blends ranged from 9.54 to 35.22. The formulated blends showed fair to good flow property.

Table .23:Precompression study of powder blend with lubricant of immediate release layer:

Drug Formulation	Bulk density* g/cm3	Tapped density* g/cm3	Compressibility index*(%)	Hausner's ratio*	Angle of repose* (degree)
R1	0.570±0.021	0.646±0.013	11.76±0.011	1.13±0.018	34.25±1.32
R2	0.544±0.026	0.612±0.017	11.11±0.032	1.125±0.025	31.41±0.22
R3	0.612±0.01	0.698±0.022	12.21±0.35	1.14±0.0047	27.10±0.57

The bulk density of IR Blends ranged from 0.544 to 0.612 $g/cm^3$and tapped densityranged from 0.612 to 0.698 g/cm^3. The compressibility index of the IR blends ranged from11.11to 12.21% and Hausner's ratio ranged from1.125 to1.14. The angle of repose of IRblends ranged from 27.10 to 34.25. The formulated IR blends with the addition of lubricant showed good flowproperty.

POST COMPRESSION STUDY

UNIFORMITY OFWEIGHT:

The uniformity of weight of the formulated tablets is given in the table

Table.24: Uniformity of weight of the formulated tablets

Formulation	Uniformity of weight(mg)*
R1	99.21
R2	97.80
R3	98.26

***MEAN±S.D (n=20)**

The tablets comply with the test for uniformity of weight[60].

TABLET THICKNESS AND DIAMETER:

The thickness and diameter of the formulated tablets is given in the table 25.

Table.25: Thickness and Diameter of the formulated tablets

Formulation	Thickness* (mm)	Diameter* (mm)
R1	2.00 ± 0.00	6.00 ± 0.00
R2	2.00 ± 0.00	6.00 ± 0.00
R3	2.00 ± 0.00	6.00 ± 0.00

***MEAN±S.D (n=05)**

The thickness and diameter of the tablets were found to be 2 mm and 6 mm respectively. The tablets have uniform thickness and diameter.

HARDNESS:

The hardness of the formulated tablets is given in the table 26.

Table.26: Hardness of the formulated tablets

Formulation	Hardness* Kg/cm^2
R1	2.50 ±0.00
R2	2.15±0.210
R3	2.20±0.244

***MEAN±S.D (n=05)**

The hardness of the tablets was found to be between 2.15 kg/cm^2 and 2.50 kg/cm^2.

FRIABILITY:

The Friability of the formulated tablets is given in the table 27

Table.27: Friability of the formulated tablets

Formulation	Friability (%)*
R1	0.872 ±0.030
R2	0.934 ±0.021
R3	0.825 ±0.024

***MEAN±S.D (n=03)**

The percentage friability of the tablets ranged from 0.825 % to 0.934 %. Hence the percentage friability complies with the official standard[60].

DRUG CONTENT:

The Drug content of the formulated IR tablets is given in the table 28 and Fig.27

Table.28: Drug content of the formulated IR tablets

Formulation	% Drug content *
R1	94.19±0.204
R2	106.20±0.346
R3	103.37±0.082

MEAN±S.D (n=03)

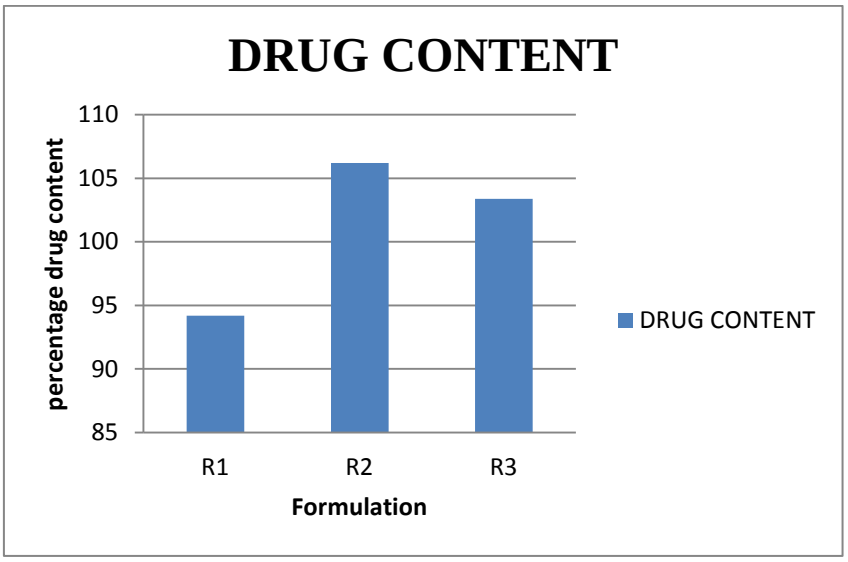


Fig.27: Drug content of the formulated IR tablets

The percentage drug content of all the formulations ranged from 94.19 % w/w to to 106.20 % w/w[60]

DISINTEGRATION TIME:

The disintegration time of the IR tablets is given in the table

Table.29: Disintegration time of the IR tablets

Formulation	Disintegration time(seconds)
R1	297
R2	35
R3	23

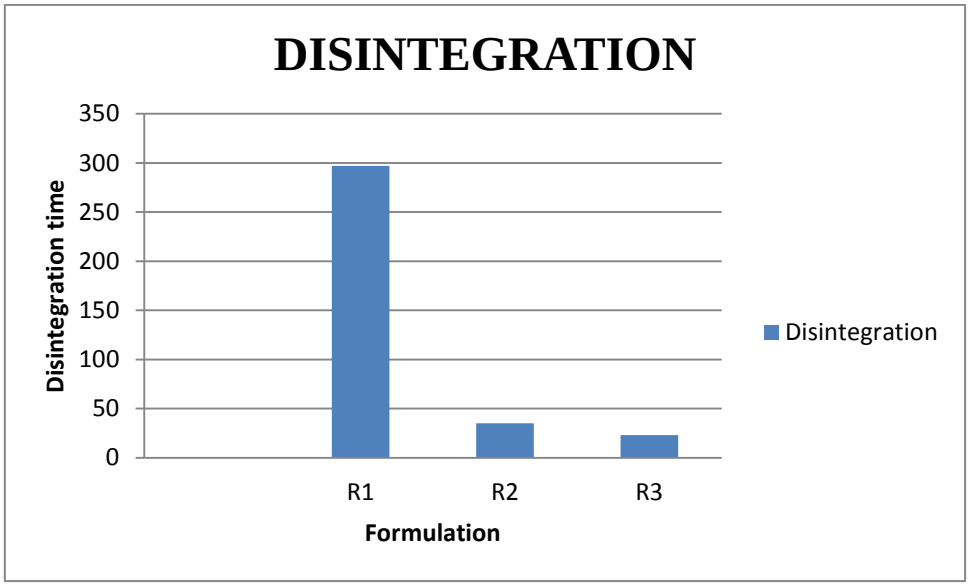


Fig.28 : Disintegration time of the IR tablets

The Disintegration time of all the formulations were ranged from 23 to 297 sec. The Formulation R3 disintegrated within 23 sec.

IN-VITRO DISSOLUTION STUDY:

The *in-vitro* dissolution of immediate release formulations of Rosuvastatin Calciumis given inthe Table.30 and Fig.29

Table.30:*In-vitro* dissolution of immediate release formulation of Rosuvastatin Calcium

Time in Minutes	Cumulative % drug release*		
	R1	**R2**	**R3**
5	19.68 ± 0.344	75.34 ±0.476	80.86 ± 0.537
10	31.35 ±0.256	86.79 ±0.237	92.79 ±0.476
15	48.06 ±0.273	92.79 ±0.569	**99.36 ± 0.582**
20	64.85 ±0.468	98.80 ±0.594	
30	70.74 ±0.449		
40	82.16 ±0.126		
50	99.13 ±0.528		
60	105.19 ±0.483		

***MEAN±S.D (n=3)**

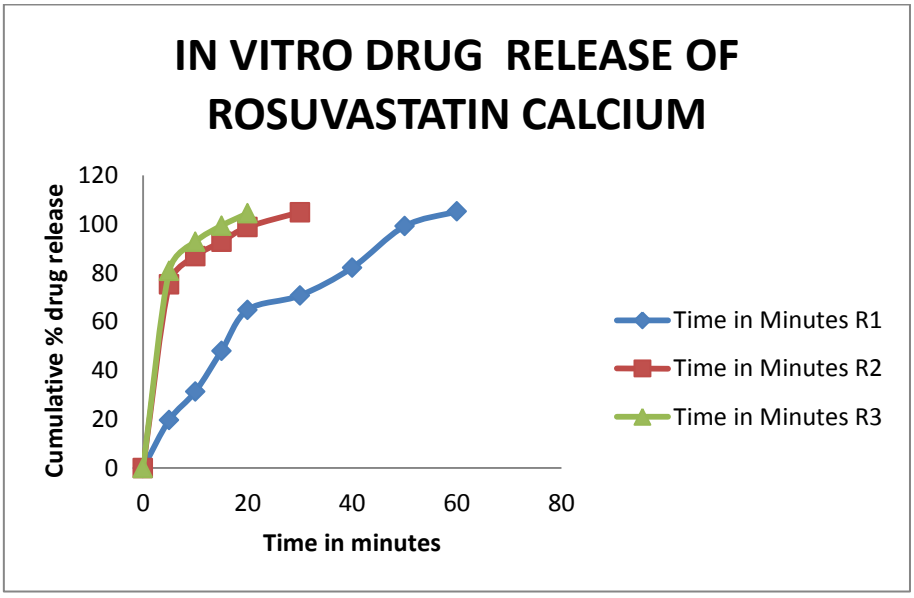


Fig.29 :*In-vitro* dissolution of immediate release formulation of Rosuvastatin calcium

From the *invitro* dissolution study the formulation R3 was found optimum and selected for bilayer floating tablets.

FOR FLOATING TABLETS:

PRECOMPRESSION STUDY:

The drug and the formulated blends of floating Carvedilol were evaluated for Precompression parameters. The results are given in the table 31.

Table Precompression study of drug and formulated blends without lubricant

Drug formulation	Bulk density* g/cm3	Tapped density* g/cm3	Compressibility index*(%)	Hausner's ratio*	Angle of repose* (degree)
Carvedilol	0.230±0.0073	0.268±0.0056	13.93 ±1.58	1.16±0.021	13.27 ±0.145
C1	0.500±0.011	0.666±0.010	24.92±1.92	1.33±0.028	35.25±1.05
C2	0.535±0.013	0.666±0.023	19.56±2.05	1.25±0.032	30.35±2.57
C3	0.526±0.021	0.666±0.018	21.06±1.39	1.26±0.025	35.39±1.22
C4	0.500±0.011	0.652±0.019	23.28±2.31	1.30±0.037	36.32±1.23
C5	0.492±0.113	0.652±0.019	24.56±0.509	1.32±0.009	43.32±0.654
C6	0.500±0.015	0.652±0.02	23.28±2.31	1.30±0.03	40.07±0.753
C7	0.492±0.011	0.666±0.016	25.12±1.70	1.33±0.03	39.39±0.655
C8	0.508±0.017	0.666±0.010	23.62±1.84	1.31±0.03	40.13±0.269

*MEAN±S.D (n=3)

The bulk density of drug and CR blend ranged from 0.230to 0.535 g/cm^{3}and tapped density ranged from 0.268 to 0.666 g/cm^3. The compressibility index of the CR blend ranged from 13.93 to 25.12% and Hausner'sratio ranged from1.16 to1.33. The angle of repose of CR blend ranged from 13.27 to 43.32. The formulated CR blend showed fair to good flow property.

Table 32.Precompression study of drug and formulated blends with lubricant

Drug formulation	Bulk density* g/cm3	Tapped density* g/cm3	Compressibility index*(%)	Hausner's ratio*	Angle of repose* (degree)
C1	0.526±0.023	0.666±0.016	21.02±0.019	1.27±0.028	33.11±0.75
C2	0.588±0.037	0.714±0.026	17.64±0.031	1.21±0.045	33.43±1.27
C3	0.526±0.015	0.625±0.030	15.84±0.038	1.19±0.041	33.50±0.59
C4	0.500±0.011	0.625±0.024	20.13±0.016	1.25±0.053	33.26±1.56
C5	0.535±0.013	0.638±0.010	16.11±0.386	1.19±0.004	41.34±0.378
C6	0.535±0.010	0.638±0.020	16.12±0.390	1.19±0.004	38.14±0.452
C7	0.526±0.025	0.638±0.027	17.57±2.440	1.22±0.040	38.46±1.10
C8	0.526±0.036	0.625±0.012	15.84±0.032	1.19±0.028	37.41±0.695

*MEAN±S.D (n=3)

The bulk density of drug and CR blend ranged from 0.500to 0.588 g/cm^{3}and tapped density ranged from 0.625 to 0.714 g/cm^3. The compressibility index of the CR blend ranged from 13.93 to 25.12% and Hausner's ratio ranged from1.16 to1.33. The angle of repose of CR blend ranged from 13.27 to 43.32. The formulated CR blend showed fair to good flow property.

POST COMPRESSION STUDIES OF CARVEDILOL FLOATING TABLETS:

UNIFORMITY OF WEIGHT:

The uniformity of weight of the floating tablets is given in the table 33.

Table.33: Uniformity of weight of the floating tablets

Formulation	Uniformity of weight(mg)*
C1	297.82
C2	297.80
C3	297.51
C4	297.90
C5	297.16
C6	297.60
C7	297.82
C8	297.96

***MEAN±S.D (n=20)**

The tablets comply with the test for uniformity of weight[60].

TABLET THICKNESS AND DIAMETER:

The thickness and diameter of the floating tablets is given in the table34 .

Table.34 : Thickness and Diameter of the floating tablets

Formulation	Thickness* (mm)	Diameter* (mm)
C1	3.00±0.00	9.00±0.00
C2	3.00±0.00	9.00±0.00
C3	3.00±0.00	9.00±0.00
C4	3.00±0.00	9.00±0.00
C5	3.00±0.00	9.00±0.00
C6	3.00±0.00	9.00±0.00
C7	3.00±0.00	9.00±0.00
C8	3.00±0.00	9.00±0.00

***MEAN±S.D (n=5)**

The thickness and diameter of the tablets were found to be 3 mm and 9 mm respectively. The tablets have uniform thickness and diameter.

HARDNESS:

The hardness of the floating tablets is given in the table35.

Table.35: Hardness of the floating tablets

Formulation	Hardness* Kg/cm^2
C1	3.3±0.244
C2	3.9±0.21
C3	4.1±0.20
C4	4.1±0.20
C5	3.5±0.12
C6	3.9±0.20
C7	4.2±0.28
C8	4.3±0.31

***MEAN±S.D (n=5)**

The hardness of the tablets was found to be between 3.3 kg/cm^{2}and 4.3 kg/cm^2

FRIABILITY:

The Friability of the floating tablets is given in the table36.

Table.36: Friability of the floating tablets

Formulation	Friability* (%)
C1	0.249± 0.0095
C2	0.228±0.0057
C3	0.203±0.0046
C4	0.194±0.0098
C5	0.235±0.0078
C6	0.212±0.0068
C7	0.198±0.0074
C8	0.187±0.0057

***MEAN±S.D (n=3)**

The percentage friability of the tablets ranged from 0.187 % to 0.249 %. Hence thepercentage friability complies with the official standard.

INVITRO FLOATING STUDIES:

The *invitro* floating characteristics of Carvedilol floating tablets is given in the Table37 and Fig 30

Table.37 :*In-vitro* floating characteristics of Carvedilol floating tablets

Formulation	Floating lag time (seconds)	Floating duration (Hours)
C1	42	>24
C2	51	>24
C3	48	>24
C4	45	>24
C5	73	>24
C6	69	>24
C7	75	>24
C8	72	>24

***MEAN±S.D (n=3)**

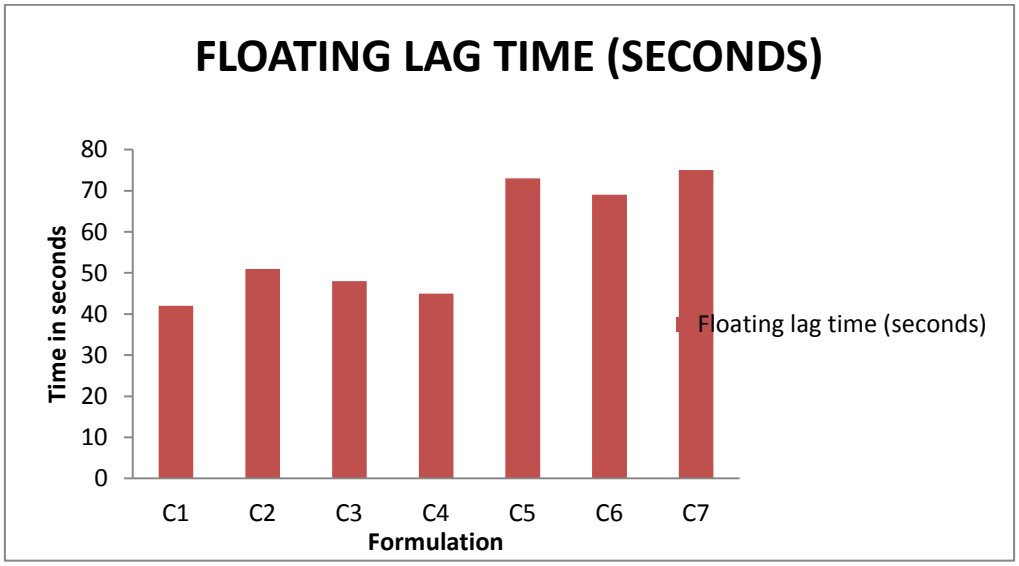


Fig.30 :*In-vitro* floating lag time of Floating tablets

The floating duration of all floating tablets was >24 hours and the floating lag time ranged from 42 –85 seconds.

DRUG CONTENT:

The drug content of Carvedilol floating tablets is given in the table38 and Fig 31.

Table.38: Drug content of floating tablet

Formulation	% Drug content
C1	97.82
C2	96.92
C3	101.6
C4	98.20
C5	97.96
C6	102.68
C7	99.74
C8	98.96

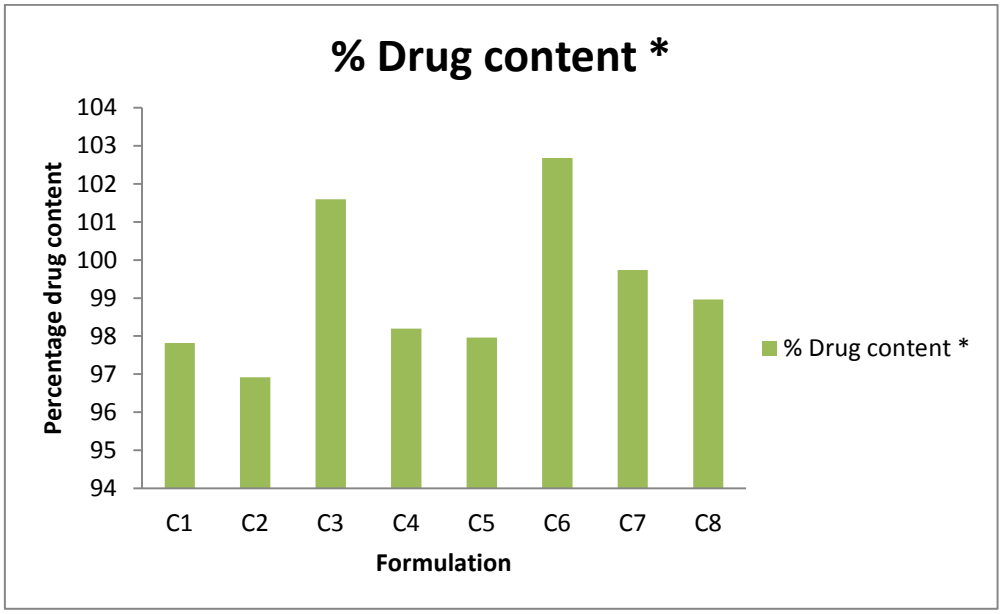


Fig.31: Drug content for formulated floating Carvedilol tablets

The percentage drug content of Carvedilolin all the formulations rangedFrom 96.92 % w/w to 102.68% w/w . All the formulations comply with the officialStandards[60].

SWELLING STUDIES OF CARVEDILOL FLOATING TABLETS:

Swelling study was carried out on the bilayer floating tablets. The % swelling of the bilayer floating tablets is given in the table 39 and fig. 32

Table 39: Swelling Index of Carvedilol floating tablets

Time in hours	% Swelling							
	C1	C2	C3	C4	C5	C6	C7	C8
0	0	0	0	0	0	0	0	0
1	42.73	45.01	47.28	48.23	34.17	35.61	35.98	37.56
2	91.69	92.73	92.85	94.32	87.72	89.46	89.57	90.85
4	156.48	156.72	158.79	159.47	140.52	142.36	146.02	148.83
6	183.61	183.83	185.30	186.49	175.21	176.96	178.59	178.82
8	221.05	224.76	226.83	227.90	209.31	216.89	217.23	219.83
10	268.74	269.23	269.58	272.34	274.82	279.31	282.73	284.67
12	304.72	305.73	309.56	314.59	297.72	299.56	301.58	305.67

The swelling index of the Carvedilol floating tablets showed that the floating matrix layer maintained their integrity and increased swelling during the study.The swelling index of the Carvedilol floating tablets ranged from 297.72 to 314.59%.

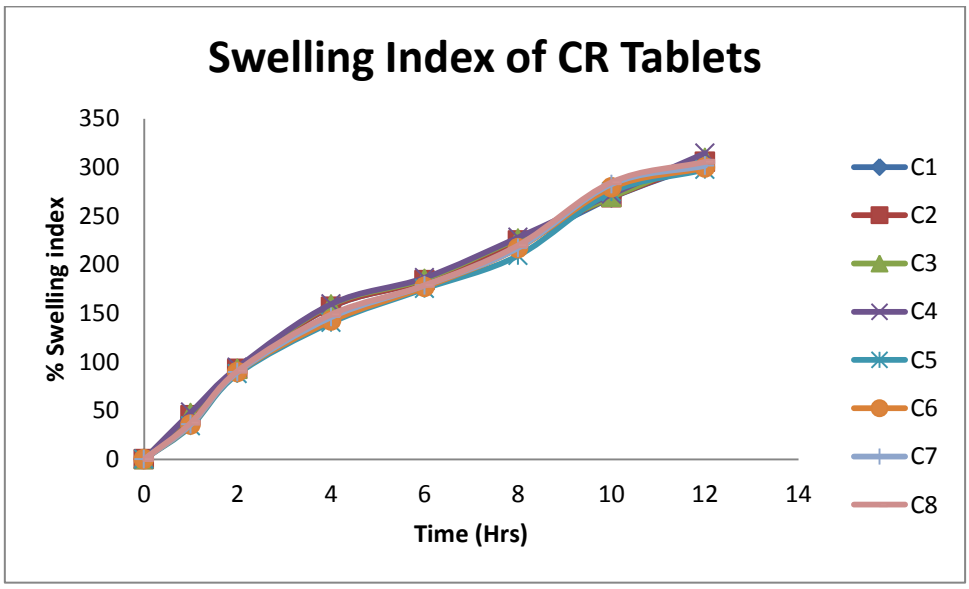


Fig. 32: Swelling index of Carvedilolfloating tablets.

***IN VITRO* DISSOLUTION STUDY:**

The *in-vitro* dissolution of Carvedilol floating tablets is given in the table.40 and fig.33

Table.40:*In-vitro* dissolution study of Carvedilol floating tablets

TIME	**CUMULATIVE % DRUG RELEASE**							
(Hours)	C1	C2	C3	C4	C5	C6	C7	C8
1	11.41	9.92	7.66	6.35	10.43	9.86	8.66	7.206
2	14.67	12.49	10.69	8.98	16.08	1.43	13.08	11.60
3	17.96	16.32	14.34	13.56	20.52	15.85	16.32	14.74
4	21.91	20.18	18.01	17.52	28.08	20.64	20.17	19.12
5	25.87	23.42	20.51	20.86	33.83	25.44	24.05	22.30
6	34.35	27.32	25.40	24.86	38.98	29.69	27.95	26.11
7	38.39	29.95	27.33	27.59	46.65	33.96	31.24	29.33
8	44.36	34.52	31.68	31.62	51.25	38.26	35.81	31.94
9	49.73	39.73	34.84	33.69	55.87	43.16	38.52	34.58
10	55.77	45.60	38.62	36.51	59.53	48.17	43.12	37.84
11	59.92	50.23	43.01	38.65	64.31	54.28	48.37	41.12
12	64.72	56.16	48.64	40.81	66.44	61.53	56.17	48.11
18	75.28	61.52	53.75	44.97	77.46	68.27	64.32	51.05
19	78.93	63.84	55.46	45.54	80.98	69.34	66.79	52.78
20	80.45	65.27	56.37	46.53	84.14	71.03	67.48	54.94
21	82.57	67.35	58.68	47.48	87.71	74.89	68.04	56.38
22	84.36	68.60	60.94	49.38	90.67	76.56	68.95	57.50
23	86.97	70.38	62.59	50.49	94.88	79.30	70.38	58.03
24	87.52	72.16	63.86	52.04	97.25	80.65	71.54	58.70

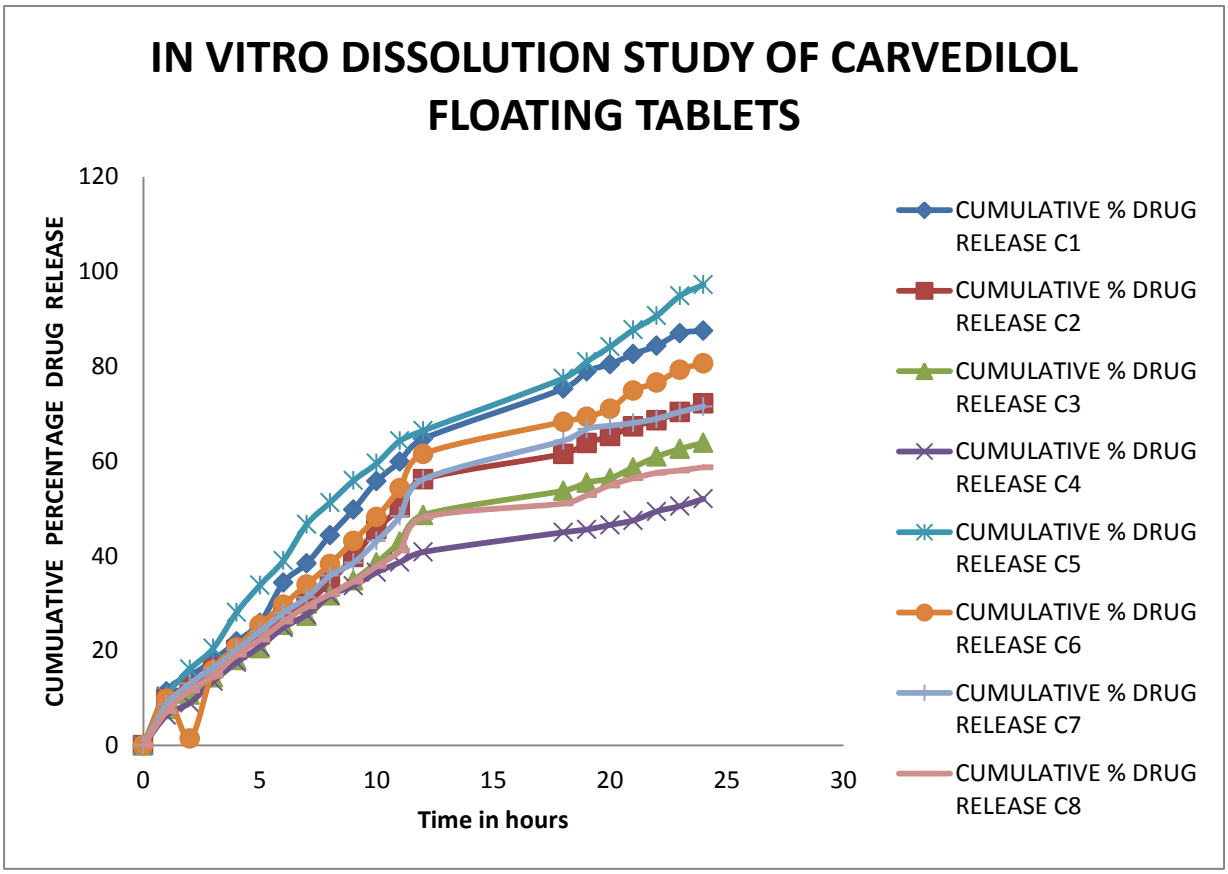


Fig.33 :*In-vitro* dissolution study of Carvedilol floating tablets

The results of *invitro* dissolution study of Gastroretentive floating tablets showed that all the formulations containing guar gum,xanthan gum and HPMC K 100 controlled the drug release more than 24 hours. Among these formulations C5 formulation containing xanthan gum polymer releases 97.25% at the end of 24 hrs. From above results the formulation C5 was found optimum and selected for bilayer floating tablets.

FORMULATION OF BILAYER FLOATING TABLETS

The optimized immediate release powder blend (R3) was compressed on the optimized floating powder blend (C5) using 10 station tablets compression machine.

POST COMPRESSION STUDY OF BILAYER FLOATING TABLETS

The compressed bilayer floating tablets were evaluated for the following parameters and values are given in table below.

Table41: Post compression study of bilayer tablets

PARAMETERS		BILAYER TABLETS
Uniformity of weight (mg)		400.06 ± 0.109
Thickness (mm)		4.00 ± 0.00
Diameter (mm)		9.00 ± 0.00
Hardness (kg/cm2)		6.36 ± 0.210
Friability (%)		0.267±0.0056
Floating lag time (secs)		78
Floating duration (hours)		>24
% Drug content	Rosuvastatin calcium	98.61
	Carvedilol	97.28

The bilayer floating tablets fulfilled the official requirement of uniformity of weight, thickness, diameter, hardness, friability and drug content was found to be within the limit[60].

IN-VITRO DRUG RELEASE STUDY OF BILAYER TABLETS

The *in-vitro* dissolution study of bilayer floating tablets is given in table .42

Table.42: *In-vitro* dissolution study of bilayer floating tablets

TIME (Hours)	CUMULATIVE % DRUG RELEASE	
	Rosuvastatin calcium	Carvedilol
0.083	61.71	-
0.16	81.87	-
0.25	99.97	-
0.33	107.13	-
0.41		-
0.5		1.03
0.75		2.97
1		7.47
2		13.3
3		21.73
4		25.71
5		33.23
6		38.55
7		46.14
8		51.22
9		56.64
10		61.77
11		67.25
12		69.54
18		71.28
19		78.74
20		83.03
21		86.69
22		88.12
23		90.84
24		98.09

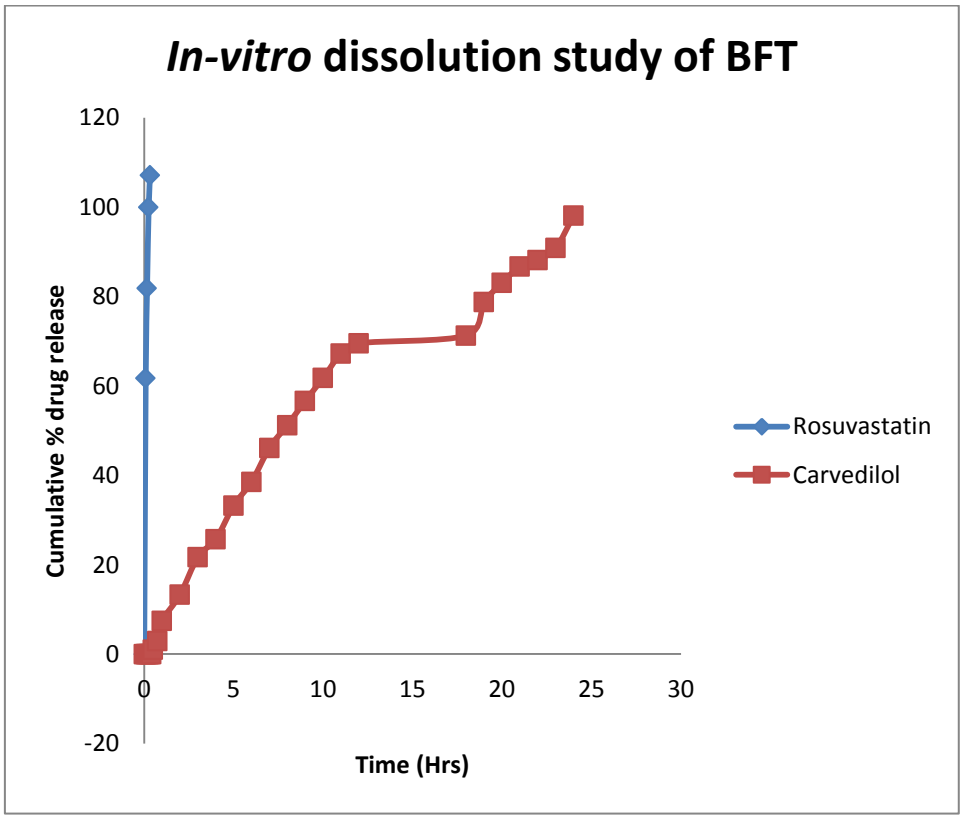


Fig.34:*In-vitro* drug release study of bilayer floating tablets

Fig. 35: Bilayer Tablets

***IN-VITRO* RELEASE KINETICS:**

The values obtained from *invitro* dissolution of from Carvedilol bilayer floating tablet were fitted in various kinetic models.

Table.43 : *In-vitro* Release Kinetics of BFT

Time in Hours	% Cum. Drug release	Log% cum. Drug release	Square root of time	Log time	% Cum. Drug remaining	Log% Cum. drug remaining	Cube root of % drug remaining
0	0	-∞	0	-∞	100	2	4.641
1	11.06	1.043	1	0	88.94	1.949	4.463
2	15.46	1.189	1.414	0.301	84.54	1.927	4.388
3	21.14	1.325	1.732	0.477	78.86	1.896	4.288
4	26.84	1.428	2	0.602	73.16	1.864	4.182
5	32.58	1.551	2.236	0.698	67.42	1.828	4.070
6	38.36	1.583	2.449	0.778	61.64	1.789	3.950
18	76.46	1.883	4.242	1.255	23.54	1.371	2.865
19	79.98	1.902	4.358	1.278	20.02	1.301	2.715
20	84.14	1.925	4.472	1.301	15.86	1.200	2.512
21	87.71	1.943	4.582	1.322	12.29	1.089	2.307
22	90.67	1.957	4.690	1.342	9.33	0.969	2.105
23	94.88	1.977	4.795	1.361	5.12	0.709	1.723
24	97.25	1.987	4.898	1.380	2.75	0.439	1.401

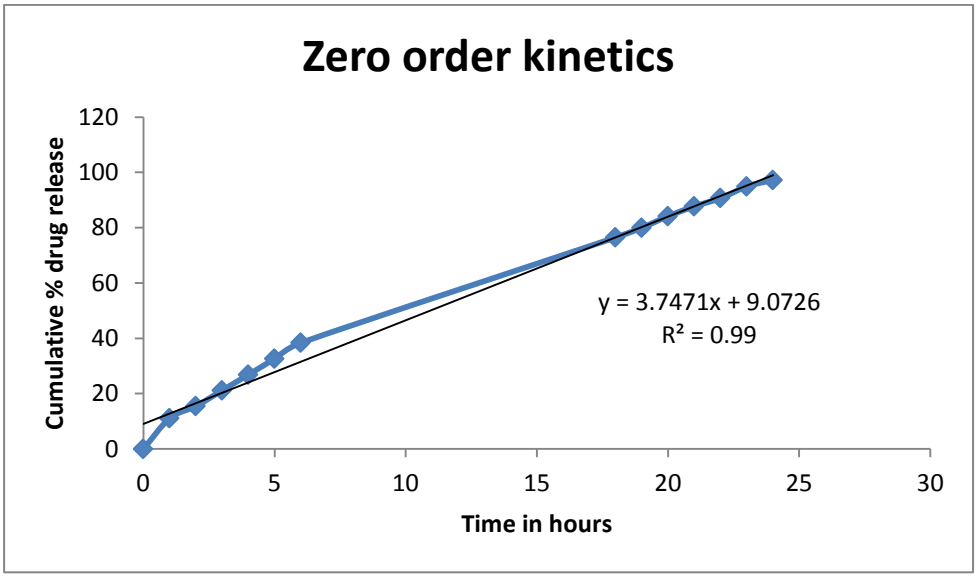


Fig.36: Zero order release kinetics

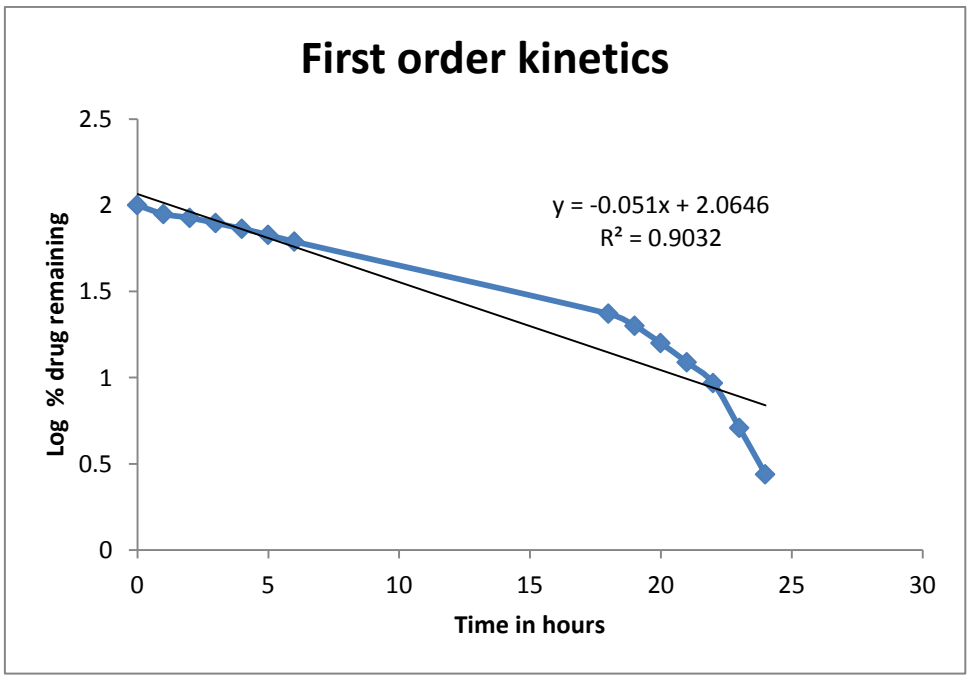


Fig. 37:First order release kinetics

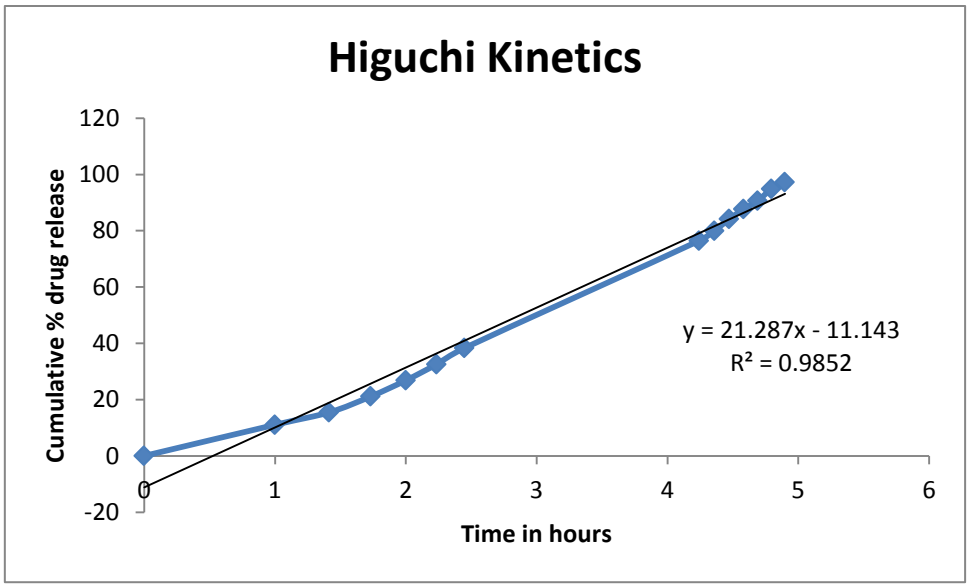


Fig.38: Higuchi kinetics

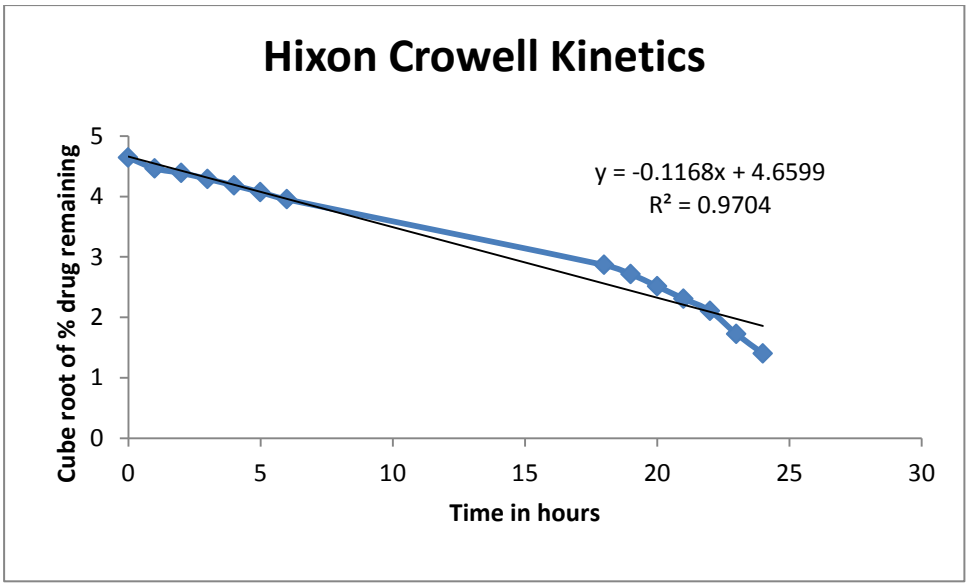


Fig.39: Hixson crowell cube root kinetics

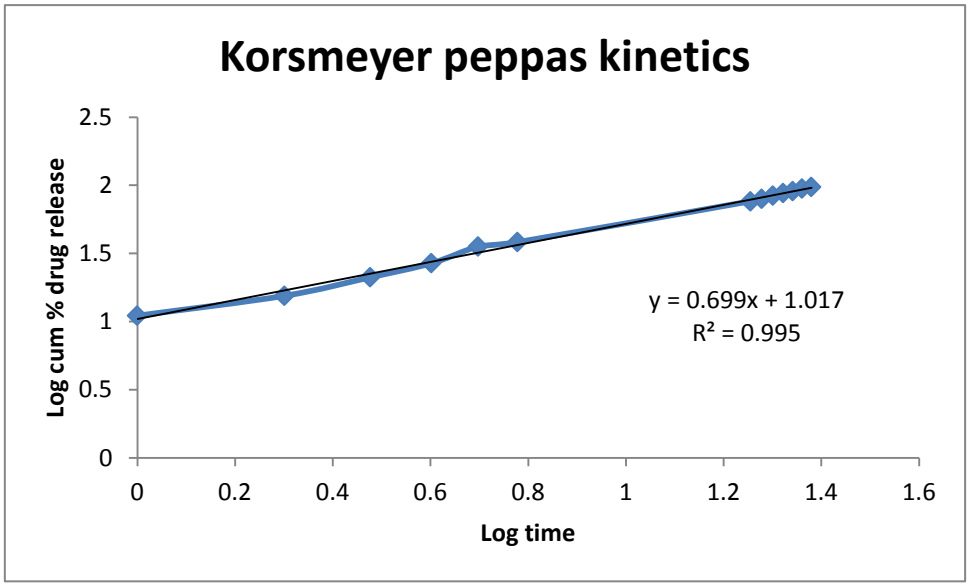


Fig. 40:Korsemeyerpeppas kinetics

Determination of drug release mechanism of bilayer floating tablets:

The co-efficient of determination(R^2) was taken as criteria for the conclusion of kinetic modelling. The R^2 values of various kinetic models are given in the table 44.

Table 44: R^2 values of various kinetic models

Kinetic model	co-efficient of determination(R^2)
Zero order	0.990
First order	0.903
Higuchi	0.970
Hixon- Crowell	0.966
Korsmeyer and Peppas	0.995

- The order of release of drug was found to be zero order, in which R2 value was close to 1

- The n value of Korsmeyer Peppas equation was found to be0.699, from that it was concluded that the release followed non- Fickian transport.

- Good correlation coefficients are obtained for Hixson Crowell cube root and Higuchi equation.

- The results showed that the formulation followed zero order release.

The present study was aimed to develop gastroretentive bilayer floating tablet containing Rosuvastatin Calcium as the immediate release layer using various super disintegrants (Sodium Starch Glycolate, Croscarmellose Sodium and Crospovidone) and Carvedilol as the controlled release layer using the natural (xanthan gum & Guar gum) and synthetic (HPMC K100) polymers.

- ✓ Physical compatibility study showed that the drug and excipients are physically compatible with each other.
- ✓ Chemical compatibility study was performed using FTIR spectroscopy and FTIR studies revealed that there was no change in major peaks thus confirming no interaction between the drug and excipients.
- ✓ Immediate release tablets and Floating tablets were formulated by direct compression method.
- ✓ The formulated blends were evaluated for precompression studies which showed that the flow property was good.
- ✓ The formulated tablets were found to be within the limits with respect to uniformity of weight, thickness, diameter, hardness and friability.
- ✓ The disintegration time of IR tablets containing Croscarmellose (R3) 2% was found to be optimum.
- ✓ The drug content of the formulated IR and CR tablets were found to be within the limits.
- ✓ Based on the *in-vitro* dissolution studies of IR tablets formulation R3 (15mins) containing Croscarmellose was optimised and selected for final bilayer tablets.
- ✓ Based on the *in vitro* dissolution studies of CR tablets, formulation C5 (24 hours) containing Xanthan gum (16.66%) and HPMC K100 (33.33%) was optimised and

selected for bilayer tablets.

- ✓ The optimised IR (R3) and CR (C5) formulations were compressed into bilayer tablets.
- ✓ The formulated bilayer tablets were found to be within the limits with respect to uniformity of weight, hardness, thickness, diameter and friability.
- ✓ The drug content of the bilayer tablets were estimated by simultaneous estimation methodand it was found to be within the pharmacopoeial limit.
- ✓ The *in vitro* dissolution studies of the optimised bilayer tablets met the IP specifications.
- ✓ The release kinetics of the optimized tablets showed that it follows zero order release kinetics. The release of the drug from the dosage form is carried out by diffusion and follows Korsmeyer peppas kinetics and the n value is greater than 0.5 indicating non-Fickian release.
- ✓ Bilayer tablet showed an initial burst effect (15mins) to provide dose of Rosuvastatin Calcium to control the blood pressure level and the controlled release of Carvedilol (24 hours) to reduce the cholesterol level.
- ✓ Combination of Rosuvastatin Calcium as an immediate release layer and Carvedilol as a controlled release layer reduces polytherapy to monotherapy and improves the patient compliance.
- ✓ The developed formulation shows an alternative to the conventional dosage form for the treatment of hypertension in patients.

FUTURE PLAN

- ➢ Scale up studies of the optimized formulation.
- ➢ *In-vivo* studies and *in vivo- in vitro* correlation studies.
- ➢ Bioequivalence studies with the marketed formulations.

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